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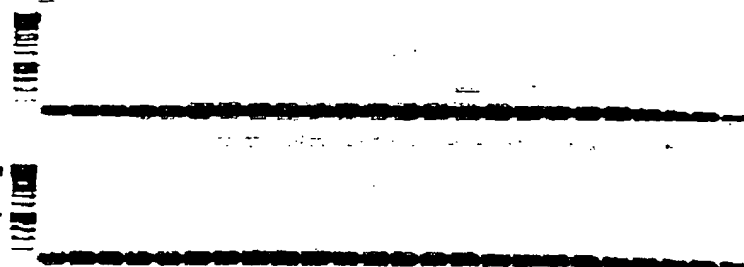
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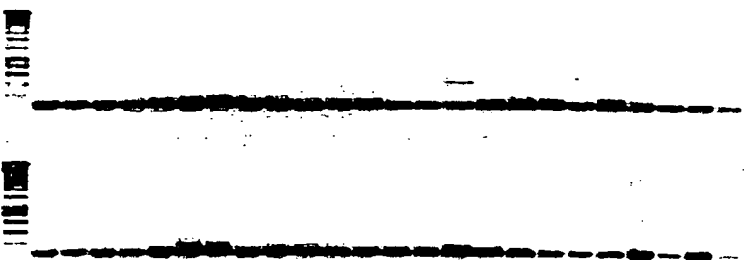
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(54) Title: TISSUE SPECIFIC GENES AND GENE CLUSTERS

XM\_061784



XM\_061785



(57) Abstract: The present invention relates to genes and genes clusters which are expressed in a tissue specific manner. For example, the invention relates to a group of genes encoding GPCR-like receptors that are involved in the function and activity of the immune system. These genes are organized into a discrete cluster at chromosomal location 1q22 (the "immune gene complex") and span about 700 kb of DNA. The region closest to the centromere comprises genes that are expressed predominantly in the thymus, while the distal region comprises genes which are expressed predominantly in the bone marrow and other hematopoietic cells. Another cluster of GPCR genes is located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in

pancreatic function. A cluster of transmembrane and GPCR-type receptor genes is also located at chromosomal band 11q12.2. These genes are expressed predominantly in the spleen (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), indicating that establishing this region of the chromosome is involved is spleen, lymphoid, and/or reticuloendothelial function. Finally, genes coding for membrane proteins have been identified which are expressed selectively in bone marrow, kidney, pancreas, and retina.

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## TISSUE SPECIFIC GENES AND GENE CLUSTERS

This application claims the benefit of U.S. Application Serial Nos. 60/372,669 April 16, 2002, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002, which are hereby incorporated by reference in their entirety.

## DESCRIPTION OF THE DRAWINGS

Figs. 1 and 2 show a physical map of the immune system gene complex. Sequence-tagged site ("STS") markers are used to characterize the chromosomal regions. An STS is defined by two short synthetic sequences (typically 20 to 25 bases each) that have been designed from a region of sequence that appears as a single-copy in the human genome (the reference numbers, and the sequences which they represent, are hereby incorporated by reference in their entirety). These sequences can be used as primers in a polymerase chain reaction (PCR) assay to determine whether the site is present or absent from a DNA sample.

Fig. 3 shows the expression pattern of transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 5 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 4 shows the expression pattern of two olfactory G-protein-coupled receptor ("GPCR") family members in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 6 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Figs. 5 (a and b) and 6 show the expression pattern in human tissues of genes selectively expressed in kidney tissue. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 11 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 7 (a-b) show organization of pancreatic gene complex on chromosome 11q24.

Fig. 8 is a schematic drawing of five of the pancreatic olfactory G-protein-coupled receptor ("GPCR") family members located in the gene complex showing regions of overlap. The numbering underneath the lines indicates amino acid position.

Fig. 9 (a and b) show the expression pattern of TMD0986, XM\_061780 (TMD0987), XM\_061781 (TMD0353), XM\_061784 (TMD0989), and XM\_061785 (TMD058) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 12 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 10 shows the expression pattern of TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), and TMD0621 (XM\_166205) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 17 indicates the SEQ ID NO for each primer ("F-oligo" is the forward primer and "R-oligo" is the reverse primer).

Fig. 11 shows the organization of the spleen gene complex on chromosome 11q12.2.

Fig. 12 (a-c) shows the expression of the pancreas genes in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 23 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Expression patterns were analyzed as described below. A twenty-four tissue panel was used (lanes from left to right): 1, adrenal gland; 2, bone marrow; 3, brain; 4, colon; 5, heart; 6, intestine; 7, pancreas; 8, liver; 9, lung; 10, lymph node; 11, lymphocytes; 12, mammary gland; 13, muscle; 14, ovary; 15, pancreas; 16, pituitary; 17, prostate; 18, skin; 19, spleen; 20, stomach; 21, testis; 22, thymus; 23, thyroid; 24, uterus. The lane at the far left of each panel contains molecular weight standards. Polyadenylated mRNA was isolated from tissue samples, and used as a template for first-strand cDNA synthesis. The resulting cDNA samples were normalized using beta-actin as a standard. For the normalization procedure, PCR was performed on aliquots of the first-strand cDNA using beta-actin specific primers. The PCR products were visualized on an ethidium bromide stained agarose gel to estimate the quantity of beta-actin cDNA present in each sample. Based on these estimates, each sample was diluted with buffer until each contained the same quantity of beta-actin cDNA per unit volume. PCR was carried out using the primers described above, and reaction



products were loaded on to an agarose (e.g., 1.5-2%) gel and separated electrophoretically.

### DESCRIPTION OF THE INVENTION

The present invention relates to tissue-selective genes and tissue-selective gene  
5 clusters. The polynucleotides and polypeptides are useful in variety of ways, including, but  
not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging,  
monitoring, prognosticating, preventing or treating, determining predisposition to, etc.,  
diseases and conditions, associated with genes of the present invention. The identification of  
specific genes, and groups of genes, expressed in pathways physiologically relevant to  
10 particular tissues, permits the definition of functional and disease pathways, and the  
delineation of targets in these pathways which are useful in diagnostic, therapeutic, and  
clinical applications. The present invention also relates to methods of using the  
polynucleotides and related products (proteins, antibodies, etc.) in business and computer-  
related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale,  
15 commercial use, licensing, etc.

#### Immune Gene Complex

The present invention relates to a group of genes involved in the function and activity  
of the immune system. These genes are organized into a discrete cluster at chromosomal  
20 location 1q22 (the "immune gene complex") and span hundreds of kb of DNA, e.g., about  
700 kb of DNA. See, Figs. 1 and 2. The region closest to the centromere comprises genes  
that are expressed predominantly in the thymus, while the distal region comprises genes  
which are expressed predominantly in the bone marrow and other hematopoietic cells.

The present invention relates to a composition consisting essentially of the 1q22  
25 immune gene complex, comprising TMD0024 (XM\_060945), TMD1779 (XM\_060946),  
TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781  
(XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890  
(XM\_060959) genes, or a fragment thereof comprising at least two said genes. As discussed  
in more detail, the composition can comprise or consist essentially of the chromosome region  
30 between STS markers that define the genomic DNA, e.g., between SHGC-81033 and SHGC-  
145403, or a fragment thereof comprising at least two said genes.

The CD1 family, a cluster of genes previously identified as coding for proteins involved in antigen presentation (Sugita and Brenner, *Seminars in Immunology*, 12:511-516, 2000), are located at the proximal boundary of the immune gene complex. The expression of CD1a, b, and c genes are restricted to professional antigen-presenting cells, including dendritic cells and some B-cell subsets (Sugita and Brenner, *ibid*). CD1d is present on other cell types, in addition to hematopoietic cells, such as intestinal cells (Sugita and Brenner, *ibid*).

Adjacent to the CD1 family, is a cluster of genes coding for transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family. These genes include XM\_060945 (TMD0024), XM\_060346 (TMD1779), XM\_060947 (TMD0884), and XM\_060948 (TMD0025), and are expressed predominantly in thymus tissues (e.g., thymocytes). XM\_089421 (TMD1781) is also expressed in thymus, but it is present in much higher amounts in lymphocytes ("PBL"). This chromosomal region can be defined by STS markers, e.g., between SHGC-81033 and D1S3249, G15944, GDB:191077, GDB:196442, RH68459, RH102597, RH69635, or RH65132, or fragments thereof, such as fragments which comprise two or more genes.

The gene for human erythroid alpha spectrin (SPTA1) is distal to the GPCR thymus-restricted family. It is expressed in bone marrow cells, and is localized to the red cell membrane (Wilmotte et al., *Blood*, 90(10):4188-96, 1997). Next to it, is another cluster of genes coding for proteins that resemble the olfactory GPCR family. These include XM\_060956 (TMD0304), XM\_060957 (TMD0888), and XM\_060959 (TMD089), and are expressed predominantly in the bone marrow, although other sites of expression are observed as well. See, e.g., Table 1. This chromosomal region can be defined by STS markers, e.g., between GDB:181583 or RH118729, and D1S2577 or SHGC-145403.

The gene for myeloid cell nuclear differentiation antigen ("MNDA") is next. MNDA is also expressed in bone marrow cells, particularly in normal and neoplastic myelomonocytic cells and a subset of normal and neoplastic B lymphocytes (Miranda et al., *Hum. Pathol.*, 30(9):1040-9, 1999).

The phrase "immune system" indicates any processes and cells which are involved in generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor,

lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells, 5 macrophages, alveolar macrophages, etc., and any precursors, progenitors, or mature stages thereof.

Table I is a summary of the genes and their expression patterns in accordance with the present invention. The genes and the polypeptides they encode can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or 10 applications associated with the tissues and cells in which they are expressed.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule 15 comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

20 In view of their selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are a useful target for histological, diagnostic, and therapeutic applications relating to the cells in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, 25 therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow and thymus tissue, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to 30 target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the

polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body).

5           The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference  
10   to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

          For example, the tissue-selective polynucleotides disclosed herein represent the  
15   configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance,  
20   a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels.  
25   The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

          While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information  
30   from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify

the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ  
5 between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue. Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

10 Binding partners can also be used as to specifically deliver therapeutic agents to a tissue of interest. For example, a gene to be delivered to a tissue can be conjugated to a binding partner (directly or through a polymer, etc.), in liposomes comprising cell surface, and then administered as appropriate to the subject who is to be treated. Additionally, cytotoxic, cytostatic, and other therapeutic agents can be delivered specifically to the tissue to  
15 treat and/or prevent any of the conditions associated with the tissue of interest.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 1, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said  
20 gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 3, 4, 8, 9, 14, 15, 22, 23, 27, 28, 35, 36, 42, 43, 49, 50, 57, and 58 (see, Table 5), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,  
25 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 1, or  
30 a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 2.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 1 (i.e., TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959)), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the

present invention, e.g., by methods of modulating the maturation of an immune system cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the maturation of an immune cell is modulated. Modulation as used throughout  
5 includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on immune system cell maturation, i.e., where modulating the gene directly effects the maturational process by modulating a gene in a immune system cell, or less directly, e.g.,  
10 where the gene is expressed in a cell-type that delivers a maturational signal to the immune system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such as positive selection, negative selection, apoptosis, recombination, expression of T-cell receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization, RAG expression, differentiation, TCR expression, antigen expression, etc. See also below  
15 and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders Company, 2000, e.g., Pages 149-160. Process include reception of a signal, such as cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the maturation, such as an antibody to a GPCR of Table 1, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also  
20 be modulated comprising, e.g., contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-lymphoid cells include accessory cells, such as antigen presenting cells, macrophages,  
25 mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types which do not normally arise from lymphoid progenitors. Interactions that can be modulated included, e.g., antigen presentation, positive selection, negative selection, progenitor cell differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above and below, for other immune system processes.

30 Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in immune system cells. Methods of

expressing a heterologous polynucleotide in immune system cells can comprise, e.g.,  
expressing a nucleic acid construct in immune system cells, said construct comprising a  
promoter sequence operably linked to said heterologous polynucleotide, wherein said  
promoter sequence is selected from Table 5. In addition to the cell lines mentioned below,  
5 the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem  
cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, antigen presenting  
cells, macrophages, and cell lines derived therefrom, cell lines such as JHK3 (CRL-10991),  
KG-1 (CCL-246), KG-1a (CCL-246.1), U-937 (CRL-1593.2), VA-ES-BJ (CRL-2138), TUR  
(CRL-2367), ELI (CRL-9854), 28SC (CRL-9855), KMA (CRL-9856), THP-1 (TIB-2002),  
10 WEHI-274.1 (CRL-1679), M-NFS-60 (CRL-1838), MH-S (CRL-2019), SR-4987 (CRL-  
2028), NCTC 3749 (CCL-461), AMJ2-C8 (CRL 2455), AMJ2-C11 (CRL2456), PMJ2-PC  
(CRL-2457), EOC2 (CRL-2467), as well as any primary and established immune system cell  
lines.

## 15 Thymus

The thymus is the site of T-cell lymphocyte maturation. Immature lymphocytes  
migrate into the thymus from the bone marrow and other organs in which they are generated.

The selection process that shape the antigen repertoire of T-cells takes place in the thymus  
organ. Both positive and negative selection processes take place. For a review, see, e.g.,

20 Abbas et al., Cellular and Molecular Immunology, 4th Edition, W.B. Saunders Company,  
2000, e.g., Pages 126-130 and 149-160.

There are various diseases and disorders related to thymus tissue, including, but not  
limited to, thymic carcinoma, thymoma, Omenn syndrome, autoimmune diseases, allergy,

25 syndrome, promoting immune system regeneration after bone marrow transplantation,  
immuno-responsiveness, etc. The thymic selective genes and polypeptides encoded thereby  
can be used to treat or diagnose any thymic condition. For instance, chemotherapeutic and  
cytotoxic agents can be conjugated to thymic selective antibodies and used to ablate a  
thymoma or carcinoma. They can be used alone or in combination with other treatments.

30 See, e.g., Graeber and Tamin, Semin. Thorac. Cardiovasc. Surg., 12:268-277, 2000; Loehrer,  
Ann. Med., 31 Suppl. 2:73-79, 1999.



## Bone marrow

All circulating blood cells in the adult, including all immature lymphocytes, are produced in the bone marrow. In addition, the bone marrow is also the site of B-cell maturation. The marrow consists of a spongelike reticular framework located between long trabeculae. It is filled with fat cells, stromal cells, and precursor hematopoietic cells. The precursors mature and exit through the vascular sinuses

All the blood cells are believed to arise from a common stem cell. Lineages that develop from this common stem cell include, e.g., myeloid and lymphoid progenitor cells. The myeloid progenitor develops into, erythrocytes (erythroid), platelets (megakaryocytic), basophils, eosinophils, granulocytes, neutrophils, and monocytes. The lymphoid progenitor is the precursor to B-lymphocytes, T-lymphocytes, and natural killer cells.

There are various diseases and disorders related to bone marrow, including, not limited to, e.g., red cell diseases, aplastic anemia (e.g., where there is a defect in the myeloid stem cell), pure red cell aplasia, white cell diseases, leukopenia, neutropenia, reactive (inflammatory) proliferation of white cells and nodes such as leukocytosis and lymphadenitis, neoplastic proliferation of white cells, malignant lymphoma, Non-Hodgkin's Lymphomas, Hodgkins disease, acute leukemias (e.g., acute lymphoblastic leukemia, acute myeloblastic leukemia, myelodysplastic syndrome), chronic myeloid leukemia, chronic leukemia, hairy cell leukemia, myeloproliferative disorders, plasma cell disorders, multiple myeloma, histiocytoses, etc.

## Immune System Selective Genes

The present invention relates to genes involved in the function and activity of the immune system. XM\_062147 (TMD0088) and XM\_061676 (TMD0045) code for seven membrane spanning polypeptides which are homologous to members of the olfactory G-protein-coupled receptor ("GPCR") family. XM\_062147 is expressed predominantly in bone marrow tissue, with no detectable expression in other tissues. XM\_061676 is also expressed predominantly in bone marrow tissue, but it is detected in peripheral blood lymphocytes, as well. As discussed in more detail below, XM\_062147 (TMD0088), XM\_061676 (TMD0045), and the polypeptides they encode, can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or applications

associated with the immune system and the cells in which they are expressed.

In view of their selectivity and display on the cell surface, the GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., B-cells and B-cell progenitors) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body). Ex vivo methods can be used to eliminate cancerous cells from the bone marrow, to modulate bone marrow cells, to prime bone marrow cells for an immune response, to expand a particular class of cells expressing XM\_062147 (TMD0088) or XM\_061676 (TMD0045), to transfer genes into said cells (e.g., Banerjee and Bertino, *Lancet Oncol.*, 3:154-158, 2002), etc.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The phrase "immune system" indicates any processes and cells which are involved in

generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor, lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-  
5 monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells, macrophages, etc., and any precursors, progenitors, or mature stages thereof.

XM\_062147 contains seven transmembrane segments. It is located on chromosomal band 11q12 within proximity to the locus for an inherited form of atopic hypersensitivity  
10 (OMIM 147050, e.g., associated with asthma, hay fever, and eczema). It has been suggested that the condition is a result of defect in the regulation of immunoglobulin E. XM\_061676 also is seven membrane spanning polypeptide. The chromosomal locus, 11p15, to which it maps is rich in genes associated with immune disorders, including Fanconi anemia, nucleoporin, myeloid leukemia, and T-cell lymphoblastic leukemia. Arthrogryposis  
15 multiplex congenita (distal type IIB) also maps closely to this chromosomal location.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 6, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said  
20 gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 67, 68, 76, and 77 (see, Table 6), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,  
25 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 6, or a  
30 mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 7.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of  
5 delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 6, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally,  
10 systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric  
15 carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT,  
20 MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also  
25 described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the present invention, e.g., by methods of modulating the maturation of an immune system cell,  
30 comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog thereof,

whereby the maturation of an immune cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on  
5 immune system cell maturation, i.e., where modulating the gene directly effects the  
maturation process by modulating a gene in a immune system cell, or less directly, e.g.,  
where the gene is expressed in a cell-type that delivers a maturational signal to the immune  
system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such  
as positive selection, negative selection, apoptosis, recombination, expression of T-cell  
10 receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization,  
RAG expression, differentiation, TCR expression, antigen expression, etc. See also below  
and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders  
Company, 2000, e.g., Pages 149-160. Processes include reception of a signal, such as  
cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the  
15 maturation, such as an antibody to a GPCR of Table 6, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also  
be modulated comprising, e.g., contacting said cells with an agent effective to modulate a  
gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog  
thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes  
20 (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-  
lymphoid cells include accessory cells, such as antigen presenting cells, macrophages,  
mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types  
which do not normally arise from lymphoid progenitors. Interactions that can be modulated  
included, e.g., antigen presentation, positive selection, negative selection, progenitor cell  
25 differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above  
and below, for other immune system processes.

Promoter sequences obtained from GPCR genes of the present invention can be  
utilized to selectively express heterologous genes in immune system cells. Methods of  
expressing a heterologous polynucleotide in immune system cells can comprise, e.g.,  
30 expressing a nucleic acid construct in immune system cells, said construct comprising a  
promoter sequence operably linked to said heterologous polynucleotide, wherein said

promoter sequence is selected from Table 6. In addition to the cell lines mentioned below, the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, B-cells, antigen presenting cells, macrophages, and cell lines derived therefrom.

5

#### Kidney Selective Genes

The present invention relates to genes and polypeptides which are selectively expressed in kidney tissues: TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736),  
10 TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108). These genes and polypeptides are expressed predominantly in kidney tissues, making them, and the polypeptides they encode, useful as selective markers for kidney tissue and function, as well as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases,  
15 disorders, or applications associated with the kidney and the cells in which they are expressed. TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108) includes both  
20 human and mammalian homologs of it. SEQ ID NOS 78-103 represent particular alleles, but the present invention relates to other alleles, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals) and homologs thereof. More information on these genes is summarized in Tables 8-11.

25

In view of their selectivity and display on the cell surface, the polypeptides and polynucleotides of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., juxtaglomerular cells which secrete renin, peritubular cells, endothelial cells, e.g., of the cortex and outer medulla, mesangial cells which secrete inflammatory mediators including NO and products of cyclooxygenase,  
30 visceral epithelial cells, parietal epithelial cells, podocytes, early proximal tubule cells which secrete, e.g., angiotensin converting enzyme and neutral endopeptidase, late distal tubule

cells that produce, e.g., prolyl endopeptidase, serine endopeptidase, carboxypeptidase, and neutral endopeptidase, renomedullary interstitial cells, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies, to identify kidney, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 9. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting kidney cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below,

such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 104, 105, 107, 108, 111, 112, 115, 116, 119, 120, 122, 123, 126, 127, 131, 132, 135, 136, 138, 139, 142, 143, 145, 146, 149, 150, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,  
5 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a kidney cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by TMD0049 (XM\_057351), TMD0190  
10 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding  
15 assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 9.

As indicated above, binding partners can be used to deliver agents specifically to the kidney, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an  
20 agent to a kidney cell can comprise, e.g., contacting a kidney cell with an agent coupled to binding partner specific for TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), whereby said  
25 agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the kidney can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried  
30 specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target),



present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, 5 TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108) can be targeted, including, e.g., juxtaglomerular, peritubular, endothelial, mesangial, visceral epithelial, parietal epithelial, podocytes, early proximal tubule, late distal tubule, renomedullary interstitial, etc.

10 Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with 15 binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired 20 purpose.

A kidney cell (see above for examples of kidney cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a kidney cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 25 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), or the biological activity of a polypeptide encoded thereby, or a mammalian homolog thereof, whereby said kidney cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, 30 amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the kidney cell can be modulated, including, e.g., glomerular filtration rate, filtration pressure, renal autoregulation (including via myogenic mechanism and tubuloglomerular feedback mechanism), tubular reabsorption, tubular secretion, and renal clearance. In addition, the transcription, translation, synthesis, degradation, expression, etc., of any secretory or polypeptide produced by a kidney cell can be modulated, including, but not limited to, renin-angiotensin activity, production and secretion of prostaglandins, nitric oxide, kallikrein, adenosine, endothelin, erythropoietin, and other hormones, enzymes, and other secretory and intracellular factors. The response of a kidney cell to stimuli can also be modulated, including, but not limited to, ligands to TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), oxygen levels, blood pressure, etc.

The present invention also relates to polypeptide detection methods for assessing kidney function, e.g., methods of assessing kidney function, comprising, detecting a polypeptide coded for by TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108), fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of kidney function. Kidney function tests are usually performed to determine whether the kidney is functioning normally as a way of diagnosing kidney disease. Various tests are commonly used, including, e.g., BUN (blood urea nitrogen), serum creatinine, estimated GFR, ability to concentrate urine, BUN/creatinine ratio, urine sodium and other electrolytes, urine NAG (N-acetyl-beta-glucosaminidase, adenosine deaminase, urinary alkaline phosphatase, serum and urine beta-2-microglobulin, serum uric acid, isotope scans, Doppler sonogram, positron emission tomography, specific gravity of urine, microalbumin, total protein, etc. Detection of TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148

(XM\_087108) provides an additional assessment tool, especially in diseases such as chronic renal failure, urinary tract infections, kidney stones, nephrotic syndrome, nephritic syndrome, kidney disease due to diabetes or high blood pressure, etc., As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired kidney function.

- 5 Values can be determined routinely, as they are for other kidney function markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in kidney cells. Methods of expressing a heterologous polynucleotide in kidney cells can comprise, e.g., expressing a nucleic acid construct in  
10 kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 106, 109, 110, 113, 114, 117, 118, 121, 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151. In addition to the cell lines mentioned below, the construct can be expressed in  
15 primary cells or in established cell lines.

### Kidney

The kidney maintains the constancy of fluids in an organism's internal environment, and is therefore of great importance in maintaining health and vitality. Each day, the kidney  
20 filters the blood, removing and concentrating toxins, metabolic wastes, and excess ions, allowing them to be excreted by the body in the form of urine. The excretory function of the kidney is performed by over one million blood units called nephrons, each a miniature blood filtering and processing unit. A nephron consists of a glomerulus, a tuft of capillaries, and a renal tubule. In addition to their excretory function, kidneys produce a number of different  
25 hormones, enzymes, and other secreted molecules, including the enzyme renin and the hormone erythropoietin. The kidney also is responsible for metabolizing vitamin D into its active form, calcitriol. For a full description of the kidney's function and structure, see, e.g., *Human Anatomy and Physiology*, Marieb, E.N., 3<sup>rd</sup> Edition, Benjamin/Cummings Publishing Company, Inc., 1995, pp 896-923.

30 The glomerulus is a high pressure capillary bed which filters out most substances smaller than large plasma proteins across the fenestrated glomerular epithelium, the

intervening basement membrane, and the podocyte-containing visceral membrane of the glomerulus capsule. The external layer of the glomerulus is called the parietal layer, consisting predominally of a squamous epithelium. This layer is structural. Underneath it, is the visceral layer which consists of the modified branching epithelial cells called podocytes.

- 5 These sit on top of the fenestrated glomerular endothelium. The glomerulus is connected to the renal tubule, a highly differentiated and long tube, having three major elements: the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule. Different regions of the tubule have different functions in absorption and secretion.

- Renal cells produce a variety of different hormones and chemicals, including,  
 10 prostaglandins, nitric oxide, kallikrein family, adenosine, endothelin family, renin, erythropoietin, aldosterone, antidiuretic hormone (vasopressin), natriuretic hormones, etc. Renin is involved in modulating blood pressure. It cleaves angiotensinogen, a plasma peptide, splitting off a fragment containing 10 amino acids called angiotensin I. Angiotensin I is cleaved by a peptidase secreted by blood vessels called angiotensin converting enzyme  
 15 (ACE), producing angiotensin II, which contains 8 amino acids. Angiotensin II has many direct effects on blood pressure. Erythropoietin stimulates red blood cell production in the bone marrow.

- TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719  
 20 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108) can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the kidney. These include, but are not limited to, diseases that affect the four basic morphologic components, glomeruli, tubules, interstitium, and blood vessels. Diseases  
 25 include, e.g., acute nephritic syndrome, nephritic syndrome, renal failure, urinary tract infections, renal stones, cystic diseases of the kidney, e.g., cystic renal dysplasia, polycystic disease (autosomal dominant and recessive types), medullary cystic disease, acquired cystic disease, renal cysts, parenchymal cysts, perihilar renal cysts (pyelocalyceal cysts, hilar lymphangitic cysts), glomerular diseases, diseases of tubules, tubulointerstitial diseases,  
 30 tumors of the kidney, such as benign tumors (cortical adenoma, renal fibroma, renomedullary interstitial cell tumor), malignant tumors (renal cell carcinoma, hypernephroma,

adenocarcinoma of kidney, Wilms' tumor, nephroblastoma, urothelial carcinoma), renal coloboma, nephroblastoma, clear cell sarcoma of kidney (CCSK), rhabdoid tumor of kidney (RTK), von Hippel-Lindau disease, oncocytoid renal cell carcinoma (RCC), renal leiomyoblastoma, etc. TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108) can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

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#### Pancreatic Gene Complex

The present invention relates to a cluster of olfactory GPCR (G-protein coupled) receptor genes located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in pancreatic function. See, Table 12. Because of their exquisite selectivity for pancreatic tissues, the pancreatic gene complex ("PGC"), and the genes which comprise it, are useful to assess pancreas tissue and function for diagnostic, prognostic, therapeutic, and research purposes.

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The spatial organization of the pancreatic gene complex ("PGC") is illustrated in Fig.

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7. It spans several hundred kilobases of chromosome 11, e.g., from about LOC160205 to LOC119954, from about LOC119944-LOC119954, and any part thereof. Within this region, is a cluster of genes coding for polypeptides which share sequence identity with the olfactory GPCR family. These include, but are not limited to, TMD0986, XM\_061780 (TMD0987), XM\_061781 (TMD0353), XM\_061784 (TMD0989), XM\_061785 (TMD058). Fig. 8

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illustrates the relationship between the lengths of the different coding sequences. As shown in the figure, XM\_061784 is shorter at its C-terminus than the other family members.

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As members of the GPCR family, the PGC genes all share a degree of amino acid sequence identity and similarity. See, Table 14 for values (% sequence identity is the first place; % sequence similarity is in parenthesis in the second place; calculations were performed using the publicly-available BLASTP pair-wise alignment program). TMD0986, XM\_061780, XM\_061781, and XM\_061785 each share about 40% sequence identity.

BLAST searching of publicly available sequences indicates that these polypeptides share less amino acid sequence identity with each other than they do with other olfactory GPCR homologs located elsewhere in the genome. Significantly higher amino acid sequence identity – 81% – is observed between the adjacent genes XM\_061784 and XM\_061785.

- 5 These genes appear to be part of a sub-cluster within PGC that share high polypeptide similarity between them.

The phrase “a gene of Table 12” which is used throughout the description include the specific sequences for the listed XM numbers as well as other human alleles, and mammalian homologs, such as murine homologs. For example, Table 14 lists several of the mouse  
10 homologs that are included in the present invention. While SEQ ID NOS. 152, 153, 162, 163, 167, 168, 171, 172, 175, and 176 may represent particular alleles, the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in a nucleotide sequence which is identified in populations of mammals).

TMD0986 (SEQ ID NO 152 and 153) is a full-length sequence of the previously  
15 identified XM\_061779. It contains an additional 117 amino acids not present in XM\_061779. The present invention relates to nucleic acids comprising or consisting essentially of this sequence in its entirety (e.g., amino acids 1-314), comprising or consisting essentially of nucleic acids coding for amino acids 1-117, and comprising or consisting essentially of fragments of nucleic acids coding for amino acids 1-117. Polypeptides  
20 encoded by these nucleic acids are also claimed, including polypeptide fragments of 1-117, such as 1-23, 79-97, 164-198, 261-274, and other extracellularly exposed peptides. In addition, the present invention relates to binding partners, such as antibodies, that bind to epitopes within amino acids 1-117 (e.g., SEQ ID NO 153).

## 25 Pancreas

Diabetes and other pancreatic disorders are a major health concern. Worldwide, it is estimated that 5-10% of the population suffers from some form of diabetes. Pancreatic cancer is the fifth leading cause of cancer-related mortality. In 2002, it was estimated that about 30,000 Americans would be diagnosed with pancreatic cancer, and 90% would die  
30 within 12 months. Despite the prevalence of pancreatic disease, the genetics and physiology of normal pancreatic function and pancreatic disease is still poorly understood.

The pancreas is a mixed gland comprised of exocrine and endocrine tissues. The exocrine portion comprises about 80-85% of the organ. It is divided into lobes by connective tissue septa, and each lobe is divided into several lobules. These lobules are composed of grape-like clusters of secretory cells that form sacs known as acini. An acinus is a functional unit of the pancreatic exocrine gland. All acini drain into interlobular ducts which merge to form the main pancreatic duct. It, in turn, joins together with the bile duct from the liver to form the common bile duct that empties into the duodenum. Pancreatic acinar cells make up more than 80% of the total volume of the pancreas and function in the secretion of the various enzymes that assist digestion in the gastrointestinal tract. Scattered among the acinar cells are approximately a million pancreatic islets ("islets of Langerhans") that secrete the pancreatic endocrine hormones. These dispersed islets comprise approximately 2% of the total volume of the pancreas.

The basic function of the pancreatic endocrine cells is to secrete certain hormones that participate in the metabolism of proteins, carbohydrates, and fats. The hormones secreted by the islets include, e.g., insulin, glucagon, somatostatin, pancreatic polypeptide, amylin, adrenomedullin, gastrin, secretin, and peptide-YY. See, also, Shimizu et al., *Endocrin.*, 139:389-396, 1998. The islets contain about four major and two minor cell types. The major cell types are alpha (glucagon producing), beta (insulin and amylin producing), delta (somatostatin producing which suppresses both insulin and glucagon release), and F (pancreatic polypeptide and adrenomedullin producing) cells. The minor cell types are D1 (produce vasoactive intestinal peptide or VIP) and enterochromaffin (produce serotonin) cells. The cells can be distinguished, e.g., by their morphology, hormonal content, and polynucleotide expression patterns.

The ability of the pancreas to respond to a wide variety of metabolic signals is conferred by an expression profile comprising a rich assortment of receptor proteins. G-protein coupled receptors have been previously identified in the pancreas, including, e.g., receptors for glucagon, secretin, CCK (e.g., Roettger et al., *J. Cell Biol.*, 130:579-590, 1995), purines (e.g., P2 purinoreceptors), gastrin, KiSS-1 peptides (e.g., Kotani et al., *J. Biol. Chem.*, 276:34631-6, 2001), adrenomedullin (Martinez et al., *Endocrin.*, 141:406, 2000), and interleukins. G-protein subunits have also been localized to the pancreas, including G-proteins which were previously associated with the olfactory epithelium. See, e.g., Zigman et

al., *Endocrin.*, 133:2508-2514, 1993. In addition, pancreatic cells express neurotrophin, neurotensin, and interleukin receptors.

As mentioned, the pancreas is sensitive to a variety of metabolic, soluble and hormonal signals involved in regulating blood sugar, modulating synthesis and release of pancreatic digestive enzymes, and other physiologically important processes involved in pancreas function. In analogy to the ability of olfactory receptors to detect odors and pheromones in the environment, the pancreatic GPCRs of the present invention can be used to "sniff" out and respond to various ligands in the blood which pass through the pancreas, including peptides, metabolites, and other biologically-active molecules. Biological activities include, but are not limited to, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), zymogen granule processing, G-protein coupling activity, etc.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., disorders associated with loss or mutation to 11q24, such as Jacobsen syndrome (OMIM #147791), cystic fibrosis, acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine



tumors, etc.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine,

5 acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed.

Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2

10 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are

15 specific for parts of the polypeptide which are exposed extracellularly as indicated in Table

14. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other  
20 tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is  
25 expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 12, or a mammalian homolog thereof, under  
30 conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and

technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 154, 155, 164, 165, 169, 170, 173, 174, 177, and 178, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,  
5 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 12, or a  
10 mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 14.

As indicated above, binding partners can be used to deliver agents specifically to the  
15 pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 12, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner,  
20 including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target),  
25 present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 12 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

30 Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.

Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 12, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 153, 163, 168, 172, or 176), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 12, fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g.,

amylase, serum lipase, serum trypsin-like immuoreactivity), studies of pancreatic structure (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin (CCK) test, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 12 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 156-161, 166, 179, or 180. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 12 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the pancreatic gene complex can be used as a source of the DNA marker (e.g., a nucleotide sequence present with PGC), including, e.g., TMD0986,

XM\_061780 (TMD0987), XM\_061781 (TMD0353), XM\_061784 (TMD0989), XM\_061785 (TMD058), and any part thereof, introns, intergenic regions, any DNA from about 29160-29310 kb of 11q24, NT\_009215, etc.

Human linkage maps can be constructed to establish a relationship between a region within 11q24 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

#### Retina Selective Gene

The present invention relates to NM\_013941 (GPCR181 or OR10C1), a multiple transmembrane spanning polypeptide which shares sequence identity with the olfactory G-protein coupled receptor (GPCR) family. Like other GPCR, NM\_013941 has seven transmembrane domains, at about amino acid positions 20-42, 54-76, 91-113, 134-156, 190-212, 233-255, and 265-287, of SEQ ID NO 182. It is located at about chromosomal band 6p21.31-22.2. There are several other GPCRs located nearby (e.g., OR2B3, AL022727; OR2J3, AL022727). NM\_013941 is highly expressed in brain tissue, at lower levels in heart, pituitary, and skin, and at minimally detectable levels in colon, small intestine, kidney, lymphocytes, and mammary gland. In the neuronal tissue, it was selectively expressed in the retina, but was not detected in any other brain tissue regions. The selective expression of NM\_013941 in the retina makes it useful as a marker for retinal tissue, e.g., in stem cell cultures and biopsy samples, as well as a diagnostic, prognostic, therapeutic, and research tool for any conditions, diseases, disorders, or applications associated with the retina and the cells in which it is expressed. NM\_013941 includes both human and mammalian homologs of it (e.g., mouse XM\_111729 which is similar to olfactory receptor MOR263-6). SEQ ID NOS. 181 and 182 represent a particular allele of NM\_013941; the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals).

The chromosomal region within which NM\_013941 is located comprises a number of genes involved in retinal function. These include, e.g., retinal cone dystrophy (OMIM 602093) which appears to be a result of mutation in guanylate cyclase activator-1A (e.g., Payne et al., *Human Molec. Genet.*, 7:273-277, 1998), retinal degeneration slow (OMIM 179605) which appears to be a defect in specific retinal protein homologous to rod outer segment protein-1, retinitis pigmentosa-7, retinitis pigmentosa-14 (OMIM 600132) which is associated with a mutation in the tubby-like protein TULP1 (e.g., Banerjee et al., *Nature Genet.*, 18:177-179, 1998; Hagstrom et al., *Nature Genet.*, 18:174-176, 1998), and others. Thus, this region appears to be important in eye function.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to retinal cells. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat retinal carcinomas (e.g., retinoblastoma) in analogy to how c-erbB-2 antibodies are used to breast cancer. See, e.g., Hayashi et al., *Invest. Ophthalmol. Vis. Sci.*, 40:265-72, 1999 for an example treating retinoblastoma using HSV-TK. Transfer of the gene into the retinal cells can be achieved by incorporating the gene into liposomes which have been made cell-selective by incorporating a NM\_013941 specific antibody into its bilayer. See, also, Wu and Wu, *J. Biol. Chem.*, 262: 4429-4432, 1987.

The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold,

5 etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting retinal cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for NM\_013941 (e.g., SEQ ID NOS 181), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and

10 detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 183 and 184, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,  
15 monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a retinal cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by NM\_013941 (e.g., SEQ ID NO 182), or a  
20 mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the  
25- retina, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a retinal cell can comprise, e.g., contacting a retinal cell with an agent coupled to binding partner specific for NM\_013941 (SEQ ID NO 182), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the retinal can be achieved in any effective manner, including by administering  
30 effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent

is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by NM\_013941 can be targeted, including, e.g., pigmented epithelial cells, photoreceptor cells, cones, rods, bipolar cells, ganglion cells, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.

Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

A retinal cell (see above for examples of retinal cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a retinal cell, comprising, e.g., contacting said cell with an agent effective to modulate NM\_013941, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 182), or a mammalian homolog thereof, whereby said retinal cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

Any activity or function of the retinal cell can be modulated, including, e.g., light reception, phototransduction, excitation of rods, excitation of cones, metabolism of vitamin A, retinal, rhodopsin, and other functional molecules, cGMP binding and hydrolysis, sodium channel flux, membrane potential, phosphodiesterase activity, G-protein activity and coupling, vitamin A processing, sodium pump activity, calcium flux, etc. The response of a retinal cell to stimuli can also be modulated, including, but not limited to, ligands to



NM\_013941, light, ion levels, second messenger levels, etc.

Promoter sequences can be utilized to selectively express heterologous genes in retinal cells. Methods of expressing a heterologous polynucleotide in retinal cells can comprise, e.g., expressing a nucleic acid construct in retinal cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is obtained from NM\_01394, e.g., on genomic NT\_007592. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

## 10 Retina

The retina is a two-layered structure located on the back of the eye. It is the primary organ responsible for vision. The outer pigmented layer is comprised of pigmented epithelial cells that absorb light, preventing it from scattering in the eye, and store vitamin A needed by the photoreceptor cells. The inner neural layer is comprised of three main cell types:

15 photoreceptor cells, bipolar cells, and ganglion cells. The local currents generated by a light stimulus spreads from the photoreceptor cells to the bipolar cells, and then on to the innermost ganglion cells. The optic disc is the exit site of the retinal ganglion axons which then bundle into the optic nerve

Photoreceptors consist of rods and cones which are the photosensitive cells of the retina. Each rod and cone elaborates a specialized cilium, called the outer segment, that contains the phototransduction machinery. The rods contain a specific light-absorbing visual pigment, rhodopsin. In humans, there are three classes of cones, each characterized by the expression of distinct visual pigments: the blue cone, green cone and red cone pigments. Each type of visual pigment protein is tuned to absorb light maximally at different wavelengths. The rod rhodopsin mediates scotopic vision (in dim light), whereas the cone pigments are responsible for photopic vision (in bright light). The red, blue and green pigments also form the basis of color vision.

NM\_013941 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the retinal. These include, but are not limited to, diseases that affect the basic morphologic components as mentioned above, e.g., the outer and inner cell layers, and the optic nerve the retina. Diseases include, e.g.,

retinal degeneration, retinal degenerations such as retinitis pigmentosa, Bardet-Biedl syndrome, Bassen-Kornzweig syndrome (abetalipoproteinemia), Best disease (vitelliform dystrophy), choroidemia, gyrate atrophy, congenital amaurosis, Refsum syndrome, Stargardt disease, Usher syndrome, macular degeneration (dry and wet forms), diabetic retinopathy, peripheral vitreoretinopathies, photic retinopathies, surgery-induced retinopathies, viral retinopathies (such as HIV retinopathy related to AIDS), ischemic retinopathies, retinal detachment, traumatic retinopathy, optic neuropathy, optic neuritis, ischemic optic neuropathy, Leber optic neuropathy, diseases of Bruch's membrane, glaucoma, cancer, retinoblastoma, cancer-associated retinopathy syndrome (CAR syndrome), melanoma-associated retinopathy (MAR), etc. NM\_013941 can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

#### Spleen Gene Cluster

The present invention relates to a cluster of transmembrane and GPCR-type receptor genes located at chromosomal band 11q12.2. The genes of the present invention are expressed predominantly in the spleen (e.g., Fig. 10, lane 19) (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), establishing this region of the chromosome as a unique gene complex involved in spleen, lymphoid, and/or reticuloendothelial function. TMD1030 and TMD0621 are highly expressed in spleen tissue, with insignificant levels in other tissues. In addition to spleen. TMD1029 and TMD1029 show significant expression in the liver and lymphocytes, as well. Because of their selectivity for spleen, lymphoid, and/or reticuloendothelial tissues, the gene complex, and the chromosomal region which comprises it, are useful to assess spleen, lymphoid, and/or reticuloendothelial tissue function and for diagnostic, prognostic, therapeutic, and research purposes. Information on the genes is summarized in Tables 15-19.

The spatial organization of the gene complex is illustrated in Fig. 11. The complex spans about at least 100 kb, from about EST markers G62658, SHGC-82134, etc. (located at the end closest to the centromere and TMD1030) to SHGC-154002, SHGC-9433, etc. (located at the end furthest from the centromere and TMD0621). All the genes have the same orientation of transcription. TMD1799 (XM\_166849) (SEQ ID NO 193-194), located at the

upper region, shows very high expression in lymphocytes, but only marginal expression in spleen, indicating that expression in lymphocytes may predominate at the boundaries of the gene complex. In the lower region, TMD1027 (XM\_166856) (SEQ ID NO 195-196), spleen expression virtually disappears, while lymph node expression becomes very high. The

5 present invention includes this entire region, and any parts thereof. For instance, the present invention includes any DNA fragments within it which confer the observed tissue specificities described herein.

The gene complex is involved in spleen, immune, and RES functions. The spleen is located in the left upper region of the abdomen. In the adult, it weights about 90-180 grams, and is about 14  
10 by 7.5 cm in size. The spleen is anatomically and functionally compartmentalized into two distinct regions, the red and white pulp. The red pulp comprises blood vessels interwoven with connective tissue ("pulp cords") that is lined with reticuloendothelial cells. It possesses a blood filtering function, removing opsonized cells and trapping abnormal red blood cells. It also is a storage reservoir for platelets and other blood cells. In the fetus, the red pulp has a hematopoietic function.

15 Inside the red pulp, is lymphoid tissue know as the white pulp. Antibodies are made inside the white pulp. Similar to other lymphatic tissues, B- and T-cell's mature inside the white pulp, where they are involved in antigen presentation and lymphocyte maturation. The white pulp is clustered around the periarteriolar lymphoid sheath, and is comprised of follicles and marginal zone.

Naive B-cells are located in the primary follicle, memory cells, macrophages, and dendritic cells  
20 in the secondary follicle, and macrophages and B-cells in the marginal zone. The integrins LFA-1 and alpha4-beta1 are involved in localization of the B-cells to the marginal zone of the white pulp (Lu and Cyster, *Science*, 297:409, 2002).

The reticuloendothelial system (RES) is a multi-organ phagocytic system involved in removing particulates from the blood. It is comprised of the spleen and liver. It has the  
25 ability to sequester inert particles and dyes. Cells of the RES system include, macrophages, liver Kuppfer cells, endothelial cells lining the sinusoids of the liver, spleen, and bone marrow, and reticular cells of lymphatic and bone marrow tissues.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc.,  
30 diseases and conditions of spleen, lymphoid, and/or reticuloendothelial tissues. These include, but are not limited to, splenomegaly, hypersplenism, hemolytic anemias, hereditary

spherocytosis, hereditary elliptocytosis, thalassemia minor and major, autoimmune hemolytic anemia, thrombocytopenia, idiopathic thrombocytopenic purpura, immunologic thrombocytopenia associated with chronic lymphocytic leukemia or systemic lupus erythematosus, TTP, leukemia, lymphoma, primary and metastatic tumors, splenic cysts, infection, inflammatory diseases, anemias, blood cancers, etc. See, Table 19 for other examples.

In view of their selectivity and display on the cell surface, the genes of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., reticuloendothelial cells, macrophages, Kupffer cells, monocytes, B-lymphocytes, T-lymphocytes, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to treat breast cancer. They can also be used to detect metastatic cells in biopsies. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. See, Table 16. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types. TMD1030 and TMD0621 are predominantly and selectively expressed in spleen tissue.

The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the tissue-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ

between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue.

Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

The present invention relates to methods of detecting spleen, lymphoid, and/or reticuloendothelial cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 197-204 listed in Table 17, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a spleen, lymphoid, and/or reticuloendothelial cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of the present invention, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface. Detection can be useful for assessing spleen integrity, e.g., when it is suspected that the spleen is damaged and undergoing deterioration. The appearance of polypeptides of the present invention in body fluids, such as blood, can indicate spleen damage, including neoplastic and/or apoptotic changes.

As indicated above, binding partners can be used to deliver agents specifically to the spleen, lymphoid, and/or reticuloendothelial tissues, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a spleen, lymphoid, and/or

reticuloendothelial cell can comprise, e.g., contacting a spleen, lymphoid, and/or reticuloendothelial cell with an agent coupled to a binding partner specific for a polypeptide coding for TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), whereby said agent is delivered to said cell. Any type of agent can  
5 be used, including, therapeutic and imaging agents. Contact with the spleen, lymphoid, and/or reticuloendothelial tissue can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parenterally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried  
10 specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD1030 (XM\_166853),  
15 TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205) can be targeted, including, e.g., reticuloendothelial cells, macrophages, Kupffer cells, lymphocytes, B-lymphocytes, T-lymphocytes, etc.

Antibodies (alone or conjugated to active agents) can be used to ablate spleen and other tissues. For instance, in diseases where splenectomy is indicated (e.g., immune  
20 thrombocytopenic purpura, autoimmune hemolytic anemia, blood cell disorders, myeloproliferative disorders, tumors, hypersplenism, etc.), antibodies to TMD1030 and TMD0621 can be used to ablate spleen tissue, or block spleen function.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.  
25 Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic imaging. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal  
30 chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The

methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

- 5           A cell (see above for examples of spleen, lymphoid, and/or reticuloendothelial cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a spleen, lymphoid, and/or reticuloendothelial cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), or the biological
- 10   activity of a polypeptide encoded thereby (e.g., SEQ ID NOS 185-192), or a mammalian homolog thereof, whereby said spleen, lymphoid, and/or reticuloendothelial cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.
- 15           Any activity or function of the spleen, lymphoid, and/or reticuloendothelial tissues can be modulated, including, e.g., immune modulation (e.g., modulating antigen presentation, antibody production and secretion, humoral and cellular responses, etc.), sequestration and removal of red blood cells, clearance of microorganisms and particular antigens from blood, migration into the marginal zone or other immune and RES compartments, etc.
- 20   The present invention also relates to polypeptide detection methods for assessing spleen, lymphoid, and/or reticuloendothelial tissue function, e.g., methods of assessing spleen, lymphoid, and/or reticuloendothelial function, comprising, detecting a polypeptide coded for by TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), fragments thereof, polymorphisms thereof, in a body fluid,
- 25   whereby the level of said polypeptide in said fluid is a measure of spleen, lymphoid, and/or reticuloendothelial function. spleen, lymphoid, and/or reticuloendothelial function tests are usually performed to determine whether the spleen, lymphoid, and/or reticuloendothelial tissue is functioning normally as a way of diagnosing spleen, lymphoid, and/or reticuloendothelial disease. Various tests are commonly used, including, e.g., 99Tc-colloid
- 30   liver-spleen scan, computed tomography, ultrasound scanning of left upper quadrant, MRI, liver enzymes, etc.



Detection of a polypeptide coded for by TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), provides an additional assessment tool, especially in diseases or disorders, such as splenomegaly, hypersplenism, or ruptured spleen, where said polypeptides can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired spleen, lymphoid, and/or reticuloendothelial function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for enzymes and other proteins in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in cells. Methods of expressing a heterologous polynucleotide in cells, e.g., spleen, lymphoid, and/or reticuloendothelial cells can comprise, e.g., expressing a nucleic acid construct in spleen, lymphoid, and/or reticuloendothelial cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 205-213. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the spleen, lymphoid, and/or reticuloendothelial tissues mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or spleen, lymphoid, and/or reticuloendothelial disease-susceptibility with the gene complex of the present invention, e.g., a nucleotide sequence present in the gene complex at 11q12.2. An association between a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the gene can be used as a source of the DNA marker, exons, introns,

intergenic regions, or any DNA from the gene cluster of the present invention at chromosomal region 11q12.2, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a spleen, lymphoid, and/or reticuloendothelial disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers.

Maps can be produced for an individual family, selected populations, patient populations, etc.

In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

The present invention also relates to methods of expressing a polynucleotide in spleen, lymphoid, and/or reticuloendothelial tissue, comprising, e.g., inserting a polynucleotide, which is operably linked to an expression control sequence, into the spleen, lymphoid, and/or reticuloendothelial gene complex at chromosomal location 11q12.2 of a target cell, and growing said cell under conditions effective to express said polynucleotide.

The polynucleotide of interest can be inserted into the target chromosomal region by any suitable method, including, e.g., by gene targeting methods, such as homologous recombination, or by random insertion methods where transformed cells are subsequently screened for insertion into the desired chromosomal site. Chromosome engineering methods are discussed in more detail below, e.g., in the section on transgenic animals. By the phrase "spleen, lymphoid, and/or reticuloendothelial gene complex," it is meant the region of the chromosome in which the cluster of genes, e.g., TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), and TMD0621 (XM\_166205), of the present invention are located. Inserting an expressible polynucleotide (e.g., a polynucleotide operably linked to a promoter sequence) into this region confers the tissue expression selectivity which is characteristic of the gene cluster. Any polynucleotide of interest can be inserted into the chromosomal region, including, e.g., polynucleotides encoding polypeptides, antisense polynucleotides, etc.

A cell comprising a polynucleotide inserted into the target chromosomal location can be utilized in vitro or in vivo, e.g., in a transgenic animal. The cell is grown under conditions

which are suitable to achieve polynucleotide expression. These conditions depend upon the cell's environment, e.g., tissue culture cell, or in the form of a transgenic animal.

#### Pancreas membrane protein genes

- 5           The present invention relates to all facets of pancreas membrane protein genes, polypeptides encoded by them, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drug discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides and polypeptides are useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting,
- 10   diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, such as pancreatic cancer, diabetes, pancreatitis, and other disorders especially relating to the pancreas and the functions its performs. The identification of specific genes, and groups of genes, expressed in pathways physiologically relevant to pancreas tissue permits the definition of functional and disease
- 15   pathways, and the delineation of targets in these pathways which are useful in diagnostic, therapeutic, and clinical applications. The present invention also relates to methods of using the polynucleotides and related products (proteins, antibodies, etc.) in business and computer-related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale, commercial use, licensing, etc.
- 20           The function, structure, and diseases of the pancreas were described previously. The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic
- 25   pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset
- 30   diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell

tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine tumors, etc.

5 For example, five different pancreatic tumor samples were examined (Nos. 1, 2, 3, 4, and 5). TMD0639 was up-regulated in about 1/5 pancreatic cancers (No. 4), TMD0645 was up-regulated in about 3/5 pancreatic cancers (Nos. 2, 3, and 5), and TMD1127 was up-regulated in about 2/5 pancreatic cancers (Nos. 1 and 4). These results indicate that the probes can be used in combination in order to maximize the detection of different types of  
10 pancreatic cancers and tumors. Thus, a sample from a patient can be assessed for expression of both TMD0645 and TMD1127 to increase the probability that the pancreas cancer will be detected.

In view of their selectivity and display on the cell surface, the membrane proteins of the present invention are useful targets for histological, diagnostic, and therapeutic  
15 applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such  
20 as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells in biopsies and other tissue samples. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or  
25 other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 21. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other  
30 tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

Table 20 is a summary of the genes of the present invention which are expressed selectively and/or predominantly in pancreas tissue. Fig. 12 is an illustration of these expression patterns. Each gene is associated with a Clone ID and Accession Number ("ACCN"). The Clone ID is an arbitrary identification number for the clone, and the accession number is the number by which it is listed in GenBank. Although specific sequences are disclosed herein, and listed in GenBank by an accession number), the present invention includes all forms of the gene, including polymorphisms, allelic variations, SNPs, splice variants, and any full-length versions when the disclosed or Genbank version is partial. For convenience, these genes, and their homologs in other species, are referred to throughout the disclosure in shorthand as "the genes of Table 20," "a gene of Table 20," "polynucleotides of Table 20," "polypeptides of Table 20," etc., because Table 20 contains a listing of the genes by accession number and clone ID.

The expression patterns of the selectively and/or predominantly expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by pancreas tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the pancreas-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal pancreas tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of pancreas-

selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of pancreas-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ between samples, albeit in ways that do not change the overall expression pattern. As a result, a complete match with a particular tissue expression profile, as shown herein, is not necessary.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 20, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include the primer sequences shown in Table 23, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,

monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 20, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 20, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 20 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintigraphic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917,

6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired  
5 purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell,  
10 comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 20, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, and 255), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating,  
15 amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase  
20 (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 20, fragments thereof, polymorphisms thereof, in a  
25 body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g., amylase, serum lipase, serum trypsin-like immunoreactivity), studies of pancreatic structure  
30 (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin



(CCK) test, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 20 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344 as shown in Table 23. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 20 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Human linkage maps can be constructed to establish a relationship between the cytogenetic locus as shown in Table 22 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified

within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers.

Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g.,

- 5 identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene responsible for the phenotype.

#### Nucleic acids

- A mammalian polynucleotide, or fragment thereof, of the present invention is a
- 10 polynucleotide having a nucleotide sequence obtainable from a natural source. When the species name is used, e.g., a human, it indicates that the polynucleotide or polypeptide is obtainable from a natural source. It therefore includes naturally-occurring normal, naturally-occurring mutant, and naturally-occurring polymorphic alleles (e.g., SNPs), differentially-spliced transcripts, splice-variants, etc. By the term "naturally-occurring," it is meant that the
- 15 polynucleotide is obtainable from a natural source, e.g., animal tissue and cells, body fluids, tissue culture cells, forensic samples. Natural sources include, e.g., living cells obtained from tissues and whole organisms, tumors, cultured cell lines, including primary and immortalized cell lines. Naturally-occurring mutations can include deletions (e.g., a truncated amino- or carboxy-terminus), substitutions, inversions, or additions of nucleotide sequence. These
- 20 genes can be detected and isolated by polynucleotide hybridization according to methods which one skilled in the art would know, e.g., as discussed below.

- A polynucleotide according to the present invention can be obtained from a variety of different sources. It can be obtained from DNA or RNA, such as polyadenylated mRNA or total RNA, e.g., isolated from tissues, cells, or whole organism. The polynucleotide can be
- 25 obtained directly from DNA or RNA, from a cDNA library, from a genomic library, etc. The polynucleotide can be obtained from a cell or tissue (e.g., from an embryonic or adult tissues) at a particular stage of development, having a desired genotype, phenotype, disease status, etc.

- The polynucleotides described herein can be partial sequences that correspond to full-
- 30 length, naturally-occurring transcripts. The present invention includes, as well, full-length polynucleotides that comprise these partial sequences, e.g., genomic DNAs and polynucleotides comprising a start and stop codon, a start codon and a polyA tail, a

transcription start and a polyA tail, etc. These sequences can be obtained by any suitable method, e.g., using a partial sequence as a probe to select a full-length cDNA from a library containing full-length inserts. A polynucleotide which "codes without interruption" refers to a polynucleotide having a continuous open reading frame ("ORF") as compared to an ORF which is interrupted by introns or other noncoding sequences.

Polynucleotides and polypeptides can be excluded as compositions from the present invention if, e.g., listed in a publicly available databases on the day this application was filed and/or disclosed in a patent application having an earlier filing or priority date than this application and/or conceived and/or reduced to practice earlier than a polynucleotide in this application.

As described herein, the phrase "an isolated polynucleotide which is SEQ ID NO," or "an isolated polynucleotide which is selected from SEQ ID NO," refers to an isolated nucleic acid molecule from which the recited sequence was derived (e.g., a cDNA derived from mRNA; cDNA derived from genomic DNA). Because of sequencing errors, typographical errors, etc., the actual naturally-occurring sequence may differ from a SEQ ID listed herein. Thus, the phrase indicates the specific molecule from which the sequence was derived, rather than a molecule having that exact recited nucleotide sequence, analogously to how a culture depository number refers to a specific cloned fragment in a cryotube.

As explained in more detail below, a polynucleotide sequence of the invention can contain the complete sequence as shown herein, degenerate sequences thereof, anti-sense, muteins thereof, genes comprising said sequences, full-length cDNAs comprising said sequences, complete genomic sequences, fragments thereof, homologs, primers, nucleic acid molecules which hybridize thereto, derivatives thereof, etc.

## Genomic

The present invention also relates genomic DNA from which the polynucleotides of the present invention can be derived. A genomic DNA coding for a human, mouse, or other mammalian polynucleotide, can be obtained routinely, for example, by screening a genomic library (e.g., a YAC library) with a polynucleotide of the present invention, or by searching nucleotide databases, such as GenBank and EMBL, for matches. Promoter and other regulatory regions (including both 5' and 3' regions, as well introns) can be identified

upstream or downstream of coding and expressed RNAs, and assayed routinely for activity, e.g., by joining to a reporter gene (e.g., CAT, GFP, alkaline phosphatase, luciferase, galactosidase). A promoter obtained from a tissue selective gene can be used, e.g., in gene therapy to obtain tissue-specific expression of a heterologous gene (e.g., coding for a therapeutic product or cytotoxin). 5' and 3' sequences (including, UTRs and introns) can be used to modulate or regulate stability, transcription, and translation of nucleic acids, including the sequence to which is attached in nature, as well as heterologous nucleic acids.

### Constructs

A polynucleotide of the present invention can comprise additional polynucleotide sequences, e.g., sequences to enhance expression, detection, uptake, cataloging, tagging, etc. A polynucleotide can include only coding sequence; a coding sequence and additional non-naturally occurring or heterologous coding sequence (e.g., sequences coding for leader, signal, secretory, targeting, enzymatic, fluorescent, antibiotic resistance, and other functional or diagnostic peptides); coding sequences and non-coding sequences, e.g., untranslated sequences at either a 5' or 3' end, or dispersed in the coding sequence, e.g., introns.

A polynucleotide according to the present invention also can comprise an expression control sequence operably linked to a polynucleotide as described above. The phrase "expression control sequence" means a polynucleotide sequence that regulates expression of a polypeptide coded for by a polynucleotide to which it is functionally ("operably") linked. Expression can be regulated at the level of the mRNA or polypeptide. Thus, the expression control sequence includes mRNA-related elements and protein-related elements. Such elements include promoters, enhancers (viral or cellular), ribosome binding sequences, transcriptional terminators, etc. An expression control sequence is operably linked to a nucleotide coding sequence when the expression control sequence is positioned in such a manner to effect or achieve expression of the coding sequence. For example, when a promoter is operably linked 5' to a coding sequence, expression of the coding sequence is driven by the promoter. Expression control sequences can include an initiation codon and additional nucleotides to place a partial nucleotide sequence of the present invention in-frame in order to produce a polypeptide (e.g., pET vectors from Promega have been designed to permit a molecule to be inserted into all three reading frames to identify the one that results

in polypeptide expression). Expression control sequences can be heterologous or endogenous to the normal gene.

A polynucleotide of the present invention can also comprise nucleic acid vector sequences, e.g., for cloning, expression, amplification, selection, etc. Any effective vector can be used. A vector is, e.g., a polynucleotide molecule which can replicate autonomously in a host cell, e.g., containing an origin of replication. Vectors can be useful to perform manipulations, to propagate, and/or obtain large quantities of the recombinant molecule in a desired host. A skilled worker can select a vector depending on the purpose desired, e.g., to propagate the recombinant molecule in bacteria, yeast, insect, or mammalian cells. The following vectors are provided by way of example. Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, Phagescript, phiX174, pBK Phagemid, pNH8A, pNH16a, pNH18Z, pNH46A (Stratagene); Bluescript KS+II (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR54 0, pRIT5 (Pharmacia). Eukaryotic: PWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene), pSVK3, PBPV, PMSG, pSVL (Pharmacia), pCR2.1/TOPO, pCRII/TOPO, pCR4/TOPO, pTrcHisB, pCMV6-XL4, etc. However, any other vector, e.g., plasmids, viruses, or parts thereof, may be used as long as they are replicable and viable in the desired host. The vector can also comprise sequences which enable it to replicate in the host whose genome is to be modified.

## 20 Hybridization

Polynucleotide hybridization, as discussed in more detail below, is useful in a variety of applications, including, in gene detection methods, for identifying mutations, for making mutations, to identify homologs in the same and different species, to identify related members of the same gene family, in diagnostic and prognostic assays, in therapeutic applications (e.g., where an antisense polynucleotide is used to inhibit expression), etc.

The ability of two single-stranded polynucleotide preparations to hybridize together is a measure of their nucleotide sequence complementarity, e.g., base-pairing between nucleotides, such as A-T, G-C, etc. The invention thus also relates to polynucleotides, and their complements, which hybridize to a polynucleotide comprising a nucleotide sequence as set forth herein and genomic sequences thereof. A nucleotide sequence hybridizing to the latter sequence will have a complementary polynucleotide strand, or act as a template for one

in the presence of a polymerase (i.e., an appropriate polynucleotide synthesizing enzyme). The present invention includes both strands of polynucleotide, e.g., a sense strand and an anti-sense strand.

Hybridization conditions can be chosen to select polynucleotides which have a  
5 desired amount of nucleotide complementarity with the nucleotide sequences set forth in  
herein and genomic sequences thereof. A polynucleotide capable of hybridizing to such  
sequence, preferably, possesses, e.g., about 70%, 75%, 80%, 85%, 87%, 90%, 92%, 95%,  
97%, 99%, or 100% complementarity, between the sequences. The present invention  
particularly relates to polynucleotide sequences which hybridize to the nucleotide sequences  
10 set forth in the attached sequence disclosure or genomic sequences thereof, under low or high  
stringency conditions. These conditions can be used, e.g., to select corresponding homologs  
in non-human species.

Polynucleotides which hybridize to polynucleotides of the present invention can be  
selected in various ways. Filter-type blots (i.e., matrices containing polynucleotide, such as  
15 nitrocellulose), glass chips, and other matrices and substrates comprising polynucleotides  
(short or long) of interest, can be incubated in a prehybridization solution (e.g., 6X SSC,  
0.5% SDS, 100 µg/ml denatured salmon sperm DNA, 5X Denhardt's solution, and 50%  
formamide), at 22-68°C, overnight, and then hybridized with a detectable polynucleotide  
probe under conditions appropriate to achieve the desired stringency. In general, when high  
20 homology or sequence identity is desired, a high temperature can be used (e.g., 65 °C). As  
the homology drops, lower washing temperatures are used. For salt concentrations, the lower  
the salt concentration, the higher the stringency. The length of the probe is another  
consideration. Very short probes (e.g., less than 100 base pairs) are washed at lower  
temperatures, even if the homology is high. With short probes, formamide can be omitted.  
25 See, e.g., *Current Protocols in Molecular Biology*, Chapter 6, Screening of Recombinant  
Libraries; Sambrook et al., *Molecular Cloning*, 1989, Chapter 9.

For instance, high stringency conditions can be achieved by incubating the blot  
overnight (e.g., at least 12 hours) with a polynucleotide probe in a hybridization solution  
containing, e.g., about 5X SSC, 0.1-0.5% SDS, 100 µg/ml denatured salmon sperm DNA and  
30 50% formamide, at 42°C, or hybridizing at 42°C in 5X SSPE, 0.1-0.5% SDS, and 50%

formamide, 100 µg/ml denatured salmon sperm DNA, and washing at 65°C in 0.1% SSC and 0.1% SDS.

Blots can be washed at high stringency conditions that allow, e.g., for less than 5% bp mismatch (e.g., wash twice in 0.1% SSC and 0.1% SDS for 30 min at 65°C), i.e.,

5 selecting sequences having 95% or greater sequence identity.

Other non-limiting examples of high stringency conditions includes a final wash at 65°C in aqueous buffer containing 30 mM NaCl and 0.5% SDS. Another example of high stringent conditions is hybridization in 7% SDS, 0.5 M NaPO<sub>4</sub>, pH 7, 1 mM EDTA at 50°C, e.g., overnight, followed by one or more washes with a 1% SDS solution at 42°C.

10 Whereas high stringency washes can allow for, e.g., less than 10%, less than 5% mismatch, etc., reduced or low stringency conditions can permit up to 20% nucleotide mismatch.

Hybridization at low stringency can be accomplished as above, but using lower formamide conditions, lower temperatures and/or lower salt concentrations, as well as longer periods of incubation time.

15 Hybridization can also be based on a calculation of melting temperature (T<sub>m</sub>) of the hybrid formed between the probe and its target, as described in Sambrook et al.. Generally, the temperature T<sub>m</sub> at which a short oligonucleotide (containing 18 nucleotides or fewer) will melt from its target sequence is given by the following equation: T<sub>m</sub> = (number of A's and T's) x 2°C + (number of C's and G's) x 4°C. For longer molecules, T<sub>m</sub> = 81.5 + 16.6  
20 log<sub>10</sub>[Na<sup>+</sup>] + 0.41(%GC) - 600/N where [Na<sup>+</sup>] is the molar concentration of sodium ions, %GC is the percentage of GC base pairs in the probe, and N is the length. Hybridization can be carried out at several degrees below this temperature to ensure that the probe and target can hybridize. Mismatches can be allowed for by lowering the temperature even further.

Stringent conditions can be selected to isolate sequences, and their complements,  
25 which have, e.g., at least about 90%, 95%, or 97%, nucleotide complementarity between the probe (e.g., a short polynucleotide of the sequences disclosed herein or genomic sequences thereof) and a target polynucleotide.

Other homologs of polynucleotides of the present invention can be obtained from mammalian and non-mammalian sources according to various methods. For example,  
30 hybridization with a polynucleotide can be employed to select homologs, e.g., as described in Sambrook et al., *Molecular Cloning*, Chapter 11, 1989. Such homologs can have varying

amounts of nucleotide and amino acid sequence identity and similarity to such polynucleotides of the present invention. Mammalian organisms include, e.g., mice, rats, monkeys, pigs, cows, etc. Non-mammalian organisms include, e.g., vertebrates, invertebrates, zebra fish, chicken, *Drosophila*, *C. elegans*, *Xenopus*, yeast such as *S. pombe*,  
5 *S. cerevisiae*, roundworms, prokaryotes, plants, *Arabidopsis*, *artemia*, viruses, etc. The degree of nucleotide sequence identity between human and mouse can be about, e.g. 70% or more, 85% or more for open reading frames, etc.

#### Alignment

10 Alignments can be accomplished by using any effective algorithm. For pairwise alignments of DNA sequences, the methods described by Wilbur-Lipman (e.g., Wilbur and Lipman, *Proc. Natl. Acad. Sci.*, 80:726-730, 1983) or Martinez/Needleman-Wunsch (e.g., Martinez, *Nucleic Acid Res.*, 11:4629-4634, 1983) can be used. For instance, if the Martinez/Needleman-Wunsch DNA alignment is applied, the minimum match can be set at  
15 9, gap penalty at 1.10, and gap length penalty at 0.33. The results can be calculated as a similarity index, equal to the sum of the matching residues divided by the sum of all residues and gap characters, and then multiplied by 100 to express as a percent. Similarity index for related genes at the nucleotide level in accordance with the present invention can be greater than 70%, 80%, 85%, 90%, 95%, 99%, or more. Pairs of protein sequences can be aligned  
20 by the Lipman-Pearson method (e.g., Lipman and Pearson, *Science*, 227:1435-1441, 1985) with k-tuple set at 2, gap penalty set at 4, and gap length penalty set at 12. Results can be expressed as percent similarity index, where related genes at the amino acid level in accordance with the present invention can be greater than 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more. Various commercial and free sources of alignment programs are  
25 available, e.g., MegAlign by DNA Star, BLAST (National Center for Biotechnology Information), BCM (Baylor College of Medicine) Launcher, etc. BLAST can be used to calculate amino acid sequence identity, amino acid sequence homology, and nucleotide sequence identity. These calculations can be made along the entire length of each of the target sequences which are to be compared.

30 After two sequences have been aligned, a "percent sequence identity" can be determined. For these purposes, it is convenient to refer to a Reference Sequence and a



Compared Sequence, where the Compared Sequence is *compared* to the Reference Sequence.

Percent sequence identity can be determined according to the following formula: Percent Identity =  $100 [1 - (C/R)]$ , wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference

- 5 Sequence and the Compared Sequence where (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence, (ii) each gap in the Reference Sequence, (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the
- 10 Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

Percent sequence identity can also be determined by other conventional methods, e.g., as described in Altschul et al., *Bull. Math. Bio.* 48: 603-616, 1986 and Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915-10919, 1992.

15

#### Specific polynucleotide probes

- A polynucleotide of the present invention can comprise any continuous nucleotide sequence described herein, sequences which share sequence identity thereto, or complements thereof. The term "probe" refers to any substance that can be used to detect, identify, isolate,
- 20 etc., another substance. A polynucleotide probe is comprised of nucleic acid can be used to detect, identify, etc., other nucleic acids, such as DNA and RNA.

- These polynucleotides can be of any desired size that is effective to achieve the specificity desired. For example, a probe can be from about 7 or 8 nucleotides to several thousand nucleotides, depending upon its use and purpose. For instance, a probe used as a
- 25 primer PCR can be shorter than a probe used in an ordered array of polynucleotide probes. Probe sizes vary, and the invention is not limited in any way by their size, e.g., probes can be from about 7-2000 nucleotides, 7-1000, 8-700, 8-600, 8-500, 8-400, 8-300, 8-150, 8-100, 8-75, 7-50, 10-25, 14-16, at least about 8, at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or more, etc. The polynucleotides can have non-naturally-occurring
- 30 nucleotides, e.g., inosine, AZT, 3TC, etc. The polynucleotides can have 100% sequence identity or complementarity to a sequence disclosed herein, or it can have mismatches or

nucleotide substitutions, e.g., 1, 2, 3, 4, or 5 substitutions. The probes can be single-stranded or double-stranded.

In accordance with the present invention, a polynucleotide can be present in a kit, where the kit includes, e.g., one or more polynucleotides, a desired buffer (e.g., phosphate, tris, etc.), detection compositions, RNA or cDNA from different tissues to be used as controls, libraries, etc. The polynucleotide can be labeled or unlabeled, with radioactive or non-radioactive labels as known in the art. Kits can comprise one or more pairs of polynucleotides for amplifying nucleic acids specific for tissue selective genes, e.g., comprising a forward and reverse primer effective in PCR. These include both sense and anti-sense orientations. For instance, in PCR-based methods (such as RT-PCR), a pair of primers are typically used, one having a sense sequence and the other having an antisense sequence.

Another aspect of the present invention is a nucleotide sequence that is specific to, or for, a selective polynucleotide. The phrases "specific for" or "specific to" a polynucleotide have a functional meaning that the polynucleotide can be used to identify the presence of one or more target genes in a sample and distinguish them from non-target genes. It is specific in the sense that it can be used to detect polynucleotides above background noise ("non-specific binding"). A specific sequence is a defined order of nucleotides (or amino acid sequences, if it is a polypeptide sequence) which occurs in the polynucleotide, e.g., in the nucleotide sequences of the present invention, and which is characteristic of that target sequence, and substantially no non-target sequences. A probe or mixture of probes can comprise a sequence or sequences that are specific to a plurality of target sequences, e.g., where the sequence is a consensus sequence, a functional domain, etc., e.g., capable of recognizing a family of related genes. Such sequences can be used as probes in any of the methods described herein or incorporated by reference. Both sense and antisense nucleotide sequences are included. A specific polynucleotide according to the present invention can be determined routinely.

A polynucleotide comprising a specific sequence can be used as a hybridization probe to identify the presence of, e.g., human or mouse polynucleotide, in a sample comprising a mixture of polynucleotides, e.g., on a Northern blot. Hybridization can be performed under high stringent conditions (see, above) to select polynucleotides (and their complements which

can contain the coding sequence) having at least 90%, 95%, 99%, etc., identity (i.e., complementarity) to the probe, but less stringent conditions can also be used. A specific polynucleotide sequence can also be fused in-frame, at either its 5' or 3' end, to various nucleotide sequences as mentioned throughout the patent, including coding sequences for enzymes, detectable markers, GFP, etc, expression control sequences, etc.

A polynucleotide probe, especially one that is specific to a polynucleotide of the present invention, can be used in gene detection and hybridization methods as already described. In one embodiment, a specific polynucleotide probe can be used to detect whether a particular tissue or cell-type is present in a target sample. To carry out such a method, a selective polynucleotide can be chosen which is characteristic of the desired target tissue. Such polynucleotide is preferably chosen so that it is expressed or displayed in the target tissue, but not in other tissues which are present in the sample. For instance, if detection of pancreas, or kidney, it may not matter whether the selective polynucleotide is expressed in other tissues, as long as it is not expressed in cells normally present in blood, e.g., peripheral blood mononuclear cells. Starting from the selective polynucleotide, a specific polynucleotide probe can be designed which hybridizes (if hybridization is the basis of the assay) under the hybridization conditions to the selective polynucleotide, whereby the presence of the selective polynucleotide can be determined.

Probes which are specific for polynucleotides of the present invention can also be prepared using involve transcription-based systems, e.g., incorporating an RNA polymerase promoter into a selective polynucleotide of the present invention, and then transcribing anti-sense RNA using the polynucleotide as a template. See, e.g., U.S. Pat. No. 5,545,522.

#### Polynucleotide composition

A polynucleotide according to the present invention can comprise, e.g., DNA, RNA, synthetic polynucleotide, peptide polynucleotide, modified nucleotides, dsDNA, ssDNA, ssRNA, dsRNA, and mixtures thereof. A polynucleotide can be single- or double-stranded, triplex, DNA:RNA, duplexes, comprise hairpins, and other secondary structures, etc. Nucleotides comprising a polynucleotide can be joined via various known linkages, e.g., ester, sulfamate, sulfamide, phosphorothioate, phosphoramidate, methylphosphonate, carbamate, etc., depending on the desired purpose, e.g., resistance to nucleases, such as

RNAse H, improved in vivo stability, etc. See, e.g., U.S. Pat. No. 5,378,825. Any desired nucleotide or nucleotide analog can be incorporated, e.g., 6-mercaptopguanine, 8-oxo-guanine, etc.

Various modifications can be made to the polynucleotides, such as attaching  
5 detectable markers (avidin, biotin, radioactive elements, fluorescent tags and dyes, energy transfer labels, energy-emitting labels, binding partners, etc.) or moieties which improve hybridization, detection, and/or stability. The polynucleotides can also be attached to solid supports, e.g., nitrocellulose, magnetic or paramagnetic microspheres (e.g., as described in U.S. Pat. No. 5,411,863; U.S. Pat. No. 5,543,289; for instance, comprising ferromagnetic,  
10 supermagnetic, paramagnetic, superparamagnetic, iron oxide and polysaccharide), nylon, agarose, diazotized cellulose, latex solid microspheres, polyacrylamides, etc., according to a desired method. See, e.g., U.S. Pat. Nos. 5,470,967, 5,476,925, and 5,478,893.

Polynucleotide according to the present invention can be labeled according to any desired method. The polynucleotide can be labeled using radioactive tracers such as  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  
15  $^3\text{H}$ , or  $^{14}\text{C}$ , to mention some commonly used tracers. The radioactive labeling can be carried out according to any method, such as, for example, terminal labeling at the 3' or 5' end using a radiolabeled nucleotide, polynucleotide kinase (with or without dephosphorylation with a phosphatase) or a ligase (depending on the end to be labeled). A non-radioactive labeling can also be used, combining a polynucleotide of the present invention with residues having  
20 immunological properties (antigens, haptens), a specific affinity for certain reagents (ligands), properties enabling detectable enzyme reactions to be completed (enzymes or coenzymes, enzyme substrates, or other substances involved in an enzymatic reaction), or characteristic physical properties, such as fluorescence or the emission or absorption of light at a desired wavelength, etc.

25

#### Nucleic acid detection methods

Another aspect of the present invention relates to methods and processes for detecting tissue selective genes. Detection methods have a variety of applications, including for diagnostic, prognostic, forensic, and research applications. To accomplish gene detection, a  
30 polynucleotide in accordance with the present invention can be used as a "probe." The term "probe" or "polynucleotide probe" has its customary meaning in the art, e.g., a polynucleotide

which is effective to identify (e.g., by hybridization), when used in an appropriate process, the presence of a target polynucleotide to which it is designed. Identification can involve simply determining presence or absence, or it can be quantitative, e.g., in assessing amounts of a gene or gene transcript present in a sample. Probes can be useful in a variety of ways, such as for diagnostic purposes, to identify homologs, and to detect, quantitate, or isolate a polynucleotide of the present invention in a test sample.

Assays can be utilized which permit quantification and/or presence/absence detection of a target nucleic acid in a sample. Assays can be performed at the single-cell level, or in a sample comprising many cells, where the assay is "averaging" expression over the entire collection of cells and tissue present in the sample. Any suitable assay format can be used, including, but not limited to, e.g., Southern blot analysis, Northern blot analysis, polymerase chain reaction ("PCR") (e.g., Saiki et al., *Science*, 241:53, 1988; U.S. Pat. Nos. 4,683,195, 4,683,202, and 6,040,166; *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, New York, 1990), reverse transcriptase polymerase chain reaction ("RT-PCR"), anchored PCR, rapid amplification of cDNA ends ("RACE") (e.g., Schaefer in *Gene Cloning and Analysis: Current Innovations*, Pages 99-115, 1997), ligase chain reaction ("LCR") (EP 320 308), one-sided PCR (Ohara et al., *Proc. Natl. Acad. Sci.*, 86:5673-5677, 1989), indexing methods (e.g., U.S. Pat. No. 5,508,169), *in situ* hybridization, differential display (e.g., Liang et al., *Nucl. Acid. Res.*, 21:3269-3275, 1993; U.S. Pat. Nos. 5,262,311, 5,599,672 and 5,965,409; WO97/18454; Prashar and Weissman, *Proc. Natl. Acad. Sci.*, 93:659-663, and U.S. Pat. Nos. 6,010,850 and 5,712,126; Welsh et al., *Nucleic Acid Res.*, 20:4965-4970, 1992, and U.S. Pat. No. 5,487,985) and other RNA fingerprinting techniques, nucleic acid sequence based amplification ("NASBA") and other transcription based amplification systems (e.g., U.S. Pat. Nos. 5,409,818 and 5,554,527; WO 88/10315), polynucleotide arrays (e.g., U.S. Pat. Nos. 5,143,854, 5,424,186, 5,700,637, 5,874,219, and 6,054,270; PCT WO 92/10092; PCT WO 90/15070), Qbeta Replicase (PCT/US87/00880), Strand Displacement Amplification ("SDA"), Repair Chain Reaction ("RCR"), nuclease protection assays, subtraction-based methods, Rapid-Scan™, etc. Additional useful methods include, but are not limited to, e.g., template-based amplification methods, competitive PCR (e.g., U.S. Pat. No. 5,747,251), redox-based assays (e.g., U.S. Pat. No. 5,871,918), Taqman-based assays (e.g., Holland et al., *Proc. Natl. Acad. Sci.*, 88:7276-7280, 1991; U.S. Pat. Nos.

5,210,015 and 5,994,063), real-time fluorescence-based monitoring (e.g., U.S. Pat. 5,928,907), molecular energy transfer labels (e.g., U.S. Pat. Nos. 5,348,853, 5,532,129, 5,565,322, 6,030,787, and 6,117,635; Tyagi and Kramer, *Nature Biotech.*, 14:303-309, 1996). Any method suitable for single cell analysis of gene or protein expression can be used, including in situ hybridization, immunocytochemistry, MACS, FACS, flow cytometry, etc. For single cell assays, expression products can be measured using antibodies, PCR, or other types of nucleic acid amplification (e.g., Brady et al., *Methods Mol. & Cell. Biol.* 2, 17-25, 1990; Eberwine et al., 1992, *Proc. Natl. Acad. Sci.*, 89, 3010-3014, 1992; U.S. Pat. No. 5,723,290). These and other methods can be carried out conventionally, e.g., as described in the mentioned publications.

Many of such methods may require that the polynucleotide is labeled, or comprises a particular nucleotide type useful for detection. The present invention includes such modified polynucleotides that are necessary to carry out such methods. Thus, polynucleotides can be DNA, RNA, DNA:RNA hybrids, PNA, etc., and can comprise any modification or substituent which is effective to achieve detection.

Detection can be desirable for a variety of different purposes, including research, diagnostic, prognostic, and forensic. For diagnostic purposes, it may be desirable to identify the presence or quantity of a polynucleotide sequence in a sample, where the sample is obtained from tissue, cells, body fluids, etc. In a preferred method as described in more detail below, the present invention relates to a method of detecting a polynucleotide comprising, contacting a target polynucleotide in a test sample with a polynucleotide probe under conditions effective to achieve hybridization between the target and probe; and detecting hybridization.

Any test sample in which it is desired to identify a polynucleotide or polypeptide thereof can be used, including, e.g., blood, urine, saliva, stool (for extracting nucleic acid, see, e.g., U.S. Pat. No. 6,177,251), swabs comprising tissue, biopsied tissue, tissue sections, cultured cells, etc.

Detection can be accomplished in combination with polynucleotide probes for other genes, e.g., genes which are expressed in other disease states, tissues, cells, such as brain, heart, kidney, spleen, thymus, liver, stomach, small intestine, colon, muscle, lung, testis, placenta, pituitary, thyroid, skin, adrenal gland, pancreas, salivary gland, uterus, ovary,

prostate gland, peripheral blood cells (T-cells, lymphocytes, etc.), embryo, breast, fat, adult and embryonic stem cells, etc.

Polynucleotides can be used in wide range of methods and compositions, including for detecting, diagnosing, staging, grading, assessing, prognosticating, etc. diseases and disorders associated with tissue selective genes, for monitoring or assessing therapeutic and/or preventative measures, in ordered arrays, etc. Any method of detecting genes and polynucleotides can be used; certainly, the present invention is not to be limited how such methods are implemented.

Along these lines, the present invention relates to methods of detecting polynucleotides of the present invention in a sample comprising nucleic acid. Such methods can comprise one or more the following steps in any effective order, e.g., contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to nucleic acid in said sample, and detecting the presence or absence of probe hybridized to nucleic acid in said sample, wherein said probe is a polynucleotide which is described herein, a polynucleotide having, e.g., about 70%, 80%, 85%, 90%, 95%, 99%, or more sequence identity thereto, effective or specific fragments thereof, or complements thereto. The detection method can be applied to any sample, e.g., cultured primary, secondary, or established cell lines, tissue biopsy, blood, urine, stool, cerebral spinal fluid, and other bodily fluids, for any purpose.

Contacting the sample with probe can be carried out by any effective means in any effective environment. It can be accomplished in a solid, liquid, frozen, gaseous, amorphous, solidified, coagulated, colloid, etc., mixtures thereof, matrix. For instance, a probe in an aqueous medium can be contacted with a sample which is also in an aqueous medium, or which is affixed to a solid matrix, or vice-versa.

Generally, as used throughout the specification, the term "effective conditions" means, e.g., the particular milieu in which the desired effect is achieved. Such a milieu, includes, e.g., appropriate buffers, oxidizing agents, reducing agents, pH, co-factors, temperature, ion concentrations, suitable age and/or stage of cell (such as, in particular part of the cell cycle, or at a particular stage where particular genes are being expressed) where cells are being used, culture conditions (including substrate, oxygen, carbon dioxide, etc.). When hybridization is the chosen means of achieving detection, the probe and sample can be

combined such that the resulting conditions are functional for said probe to hybridize specifically to nucleic acid in said sample.

The phrase "hybridize specifically" indicates that the hybridization between single-stranded polynucleotides is based on nucleotide sequence complementarity. The effective  
5 conditions are selected such that the probe hybridizes to a preselected and/or definite target nucleic acid in the sample. For instance, if detection of a polynucleotide set forth herein is desired, a probe can be selected which can hybridize to such target gene under high stringent conditions, without significant hybridization to other genes in the sample. To detect  
10 homologs of a polynucleotide set forth in herein, the effective hybridization conditions can be less stringent, and/or the probe can comprise codon degeneracy, such that a homolog is detected in the sample.

As already mentioned, the methods can be carried out by any effective process, e.g., by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, *in situ* hybridization, etc., as indicated above. When PCR based techniques are  
15 used, two or more probes are generally used. One probe can be specific for a defined sequence which is characteristic of a selective polynucleotide, but the other probe can be specific for the selective polynucleotide, or specific for a more general sequence, e.g., a sequence such as polyA which is characteristic of mRNA, a sequence which is specific for a promoter, ribosome binding site, or other transcriptional features, a consensus sequence (e.g.,  
20 representing a functional domain). For the former aspects, 5' and 3' probes (e.g., polyA, Kozak, etc.) are preferred which are capable of specifically hybridizing to the ends of transcripts. When PCR is utilized, the probes can also be referred to as "primers" in that they can prime a DNA polymerase reaction.

In addition to testing for the presence or absence of polynucleotides, the present  
25 ~~invention also~~ relates to determining the amounts at which polynucleotides of the present invention are expressed in sample and determining the differential expression of such polynucleotides in samples.. Such methods can involve substantially the same steps as described above for presence/absence detection, e.g., contacting with probe, hybridizing, and detecting hybridized probe, but using more quantitative methods and/or comparisons to  
30 standards.



The amount of hybridization between the probe and target can be determined by any suitable methods, e.g., PCR, RT-PCR, RACE PCR, Northern blot, polynucleotide microarrays, Rapid-Scan, etc., and includes both quantitative and qualitative measurements. For further details, see the hybridization methods described above and below. Determining

5 by such hybridization whether the target is differentially expressed (e.g., up-regulated or down-regulated) in the sample can also be accomplished by any effective means. For instance, the target's expression pattern in the sample can be compared to its pattern in a known standard, such as in a normal tissue, or it can be compared to another gene in the same sample. When a second sample is utilized for the comparison, it can be a sample of normal  
10 tissue that is known not to contain diseased cells. The comparison can be performed on samples which contain the same amount of RNA (such as polyadenylated RNA or total RNA), or, on RNA extracted from the same amounts of starting tissue. Such a second sample can also be referred to as a control or standard. Hybridization can also be compared to a second target in the same tissue sample. Experiments can be performed that determine a  
15 ratio between the target nucleic acid and a second nucleic acid (a standard or control), e.g., in a normal tissue. When the ratio between the target and control are substantially the same in a normal and sample, the sample is determined or diagnosed not to contain cells. However, if the ratio is different between the normal and sample tissues, the sample is determined to contain, e.g., kidney, pancreas, or immune cells. The approaches can be combined, and one  
20 or more second samples, or second targets can be used. Any second target nucleic acid can be used as a comparison, including "housekeeping" genes, such as beta-actin, alcohol dehydrogenase, or any other gene whose expression does not vary depending upon the disease status of the cell.

25 Methods of identifying polymorphisms, mutations, etc.

Polynucleotides of the present invention can also be utilized to identify mutant alleles, SNPs, gene rearrangements and modifications, and other polymorphisms of the wild-type gene. Mutant alleles, polymorphisms, SNPs, etc., can be identified and isolated from subjects with diseases that are known, or suspected to have, a genetic component.

30 Identification of such genes can be carried out routinely (see, above for more guidance), e.g., using PCR, hybridization techniques, direct sequencing, mismatch reactions (see, e.g.,

above), RFLP analysis, SSCP (e.g., Orita et al., *Proc. Natl. Acad. Sci.*, 86:2766, 1992), etc., where a polynucleotide having a sequence selected from the polynucleotides of the present invention is used as a probe. The selected mutant alleles, SNPs, polymorphisms, etc., can be used diagnostically to determine whether a subject has, or is susceptible to a disorder

5 associated with tissue selective genes disclosed herein, as well as to design therapies and predict the outcome of the disorder. Methods involve, e.g., diagnosing a disorder or determining susceptibility to a disorder, comprising, detecting the presence of a mutation in a gene represented by a polynucleotide selected from the sequences disclosed herein. The detecting can be carried out by any effective method, e.g., obtaining cells from a subject, 10 determining the gene sequence or structure of a target gene (using, e.g., mRNA, cDNA, genomic DNA, etc), comparing the sequence or structure of the target gene to the structure of the normal gene, whereby a difference in sequence or structure indicates a mutation in the gene in the subject. Polynucleotides can also be used to test for mutations, SNPs, polymorphisms, etc., e.g., using mismatch DNA repair technology as described in U.S. Pat. No. 5,683,877; U.S. Pat. No. 5,656,430; Wu et al., *Proc. Natl. Acad. Sci.*, 89:8779-8783, 15 1992.

The present invention also relates to methods of detecting polymorphisms in tissue selective genes, comprising, e.g., comparing the structure of: genomic DNA comprising all or part of a tissue selective gene, mRNA comprising all or part of a tissue selective gene, cDNA 20 comprising all or part of a tissue selective gene, or a polypeptide comprising all or part of a tissue selective gene, with the structure the polynucleotides set forth herein. The methods can be carried out on a sample from any source, e.g., cells, tissues, body fluids, blood, urine, stool, hair, egg, sperm, cerebral spinal fluid, biopsy samples, serum, etc.

These methods can be implemented in many different ways. For example, 25 "comparing the structure" steps include, but are not limited to, comparing restriction maps, nucleotide sequences, amino acid sequences, RFLPs, Dnase sites, DNA methylation fingerprints (e.g., U.S. Pat. No. 6,214,556), protein cleavage sites, molecular weights, electrophoretic mobilities, charges, ion mobility, etc., between standard and a test genes. The term "structure" can refer to any physical characteristics or configurations which can be used 30 to distinguish between nucleic acids and polypeptides. The methods and instruments used to accomplish the comparing step depends upon the physical characteristics which are to be

compared. Thus, various techniques are contemplated, including, e.g., sequencing machines (both amino acid and polynucleotide); electrophoresis, mass spectrometer (U.S. Pat. Nos. 6,093,541, 6,002,127), liquid chromatography, HPLC, etc.

To carry out such methods, "all or part" of the gene or polypeptide can be compared.

- 5 For example, if nucleotide sequencing is utilized, the entire gene can be sequenced, including promoter, introns, and exons, or only parts of it can be sequenced and compared, e.g., exon 1, exon 2, etc.

### Mutagenesis

- 10 Mutated polynucleotide sequences of the present invention are useful for various purposes, e.g., to create mutations of the polypeptides they encode, to identify functional regions of genomic DNA, to produce probes for screening libraries, etc. Mutagenesis can be carried out routinely according to any effective method, e.g., oligonucleotide-directed (Smith, M., *Ann. Rev. Genet.* 19:423-463, 1985), degenerate oligonucleotide-directed (Hill et al.,  
15 *Method Enzymology*, 155:558-568, 1987), region-specific (Myers et al., *Science*, 229:242-246, 1985; Derbyshire et al., *Gene*, 46:145, 1986; Ner et al., *DNA*, 7:127, 1988), linker-scanning (McKnight and Kingsbury, *Science*, 217:316-324, 1982), directed using PCR, recursive ensemble mutagenesis (Arkin and Yourvan, *Proc. Natl. Acad. Sci.*, 89:7811-7815, 1992), random mutagenesis (e.g., U.S. Pat. Nos. 5,096,815; 5,198,346; and 5,223,409), site-  
20 directed mutagenesis (e.g., Walder et al., *Gene*, 42:133, 1986; Bauer et al., *Gene*, 37:73, 1985; Craik, *Bio Techniques*, January 1985, 12-19; Smith et al., *Genetic Engineering: Principles and Methods*, Plenum Press, 1981), phage display (e.g., Lowman et al., *Biochem.* 30:10832-10837, 1991; Ladner et al., U.S. Pat. No. 5,223,409; Huse, WIPO Publication WO 92/06204), etc. Desired sequences can also be produced by the assembly of target sequences  
25 using mutually priming oligonucleotides (Uhlmann, *Gene*, 71:29-40, 1988). For directed mutagenesis methods, analysis of the three-dimensional structure of the polypeptide can be used to guide and facilitate making mutants which effect polypeptide activity. Sites of substrate-enzyme interaction or other biological activities can also be determined by analysis of crystal structure as determined by such techniques as nuclear magnetic resonance,  
30 crystallography or photoaffinity labeling. See, for example, de Vos et al., *Science* 255:306-312, 1992; Smith et al., *J. Mol. Biol.* 224:899-904, 1992; Wlodaver et al., *FEBS Lett.*

309:59-64, 1992.

In addition, libraries of genes and fragments thereof can be used for screening and selection of genes variants. For instance, a library of coding sequences can be generated by treating a double-stranded DNA with a nuclease under conditions where the nicking occurs, e.g., only once per molecule, denaturing the double-stranded DNA, renaturing it to for double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single-stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting DNAs into an expression vector. By this method, expression libraries can be made comprising "mutagenized" tissue selective genes. The entire coding sequence or parts thereof can be used.

Polynucleotide expression, polypeptides produced thereby, and specific-binding partners thereto.

A polynucleotide according to the present invention can be expressed in a variety of different systems, in vitro and in vivo, according to the desired purpose. For example, a polynucleotide can be inserted into an expression vector, introduced into a desired host, and cultured under conditions effective to achieve expression of a polypeptide coded for by the polynucleotide, to search for specific binding partners. Effective conditions include any culture conditions which are suitable for achieving production of the polypeptide by the host cell, including effective temperatures, pH, medium, additives to the media in which the host cell is cultured (e.g., additives which amplify or induce expression such as butyrate, or methotrexate if the coding polynucleotide is adjacent to a dhfr gene), cycloheximide, cell densities, culture dishes, etc. A polynucleotide can be introduced into the cell by any effective method including, e.g., naked DNA, calcium phosphate precipitation, electroporation, injection, DEAE-Dextran mediated transfection, fusion with liposomes, association with agents which enhance its uptake into cells, viral transfection. A cell into which a polynucleotide of the present invention has been introduced is a transformed host cell. The polynucleotide can be extrachromosomal or integrated into a chromosome(s) of the host cell. It can be stable or transient. An expression vector is selected for its compatibility with the host cell. Host cells include, mammalian cells, e.g., COS, CV1, BHK, CHO, HeLa, LTK, NIH 3T3, insect cells, such as Sf9 (*S. frugipeda*) and *Drosophila*, bacteria, such as *E.*

coli, Streptococcus, bacillus, yeast, such as *Sacharomyces*, *S. cerevisiae*, fungal cells, plant cells, embryonic or adult stem cells (e.g., mammalian, such as mouse or human),

immune system cell lines, HH (ATCC CRL 2105), MOLT-4 (ATCC CRL 1582), MJ (ATCC CRL-8294), SK7 (ATCC HB-8584), SK8 (ATCC HB-8585), HM1 (HB-8586), H9

5 (ATCC HTB-176), HuT 78 (ATCC TIB-161), HuT 102 (ATCC TIB-162), Jurkat,

B-cell lines, B-cell precursor lines, NALM-36, B-cell and other lymphocyte lines immortalized with Epstein-Barr virus (transformed B lymphoblastoid), stromal cell lines, myelomas, HBM-Noda, WEHI231,

reticuloendothelial cells, endothelial cells, white blood cells, macrophages, antigen-  
10 resending cells, lymphocytes, GDM-1 (ATCC CRL-2627), THP-1 (ATCC TIB-202), HL-60 (ATCC CCL-240), and derivatives thereof, including primary and established cell lines thereof,

kidney cell lines, 293, G-402 (ATCC CRL-1440), ACHN (ATCC CRL-1611), Vero (ATCC CCL-81), 786-O (ATCC CRL-1932), 769-P (ATCC CRL-1933), CCD 1103 KIDTr (ATCC CRL-2304), CCD 1105 KIDTr (ATCC CRL-2305), Hs 835.T (ATCC CRL-7569),  
15 Hs 926.T (ATCC CRL-7678), Caki-1 (ATCC HTB-46), Caki-2 (ATCC HTB-47), SW 839 (ATCC HTB-49), LLC-MK2 (ATCC CCL-7), BHK-21 (ATCC CCL-10), MDCK, CV-1, (ATCC CRL-1573), KNRK (ATCC CRL-1569), NRK-49F (ATCC CRL-1570), A-704 (ATCC HTB-45), etc., established and primary kidney cells,

20 pancreas cell lines, , insulinoma cell lines, INS-H1, MIN6N8, RIN 1046-38, RIN-5AH, RIN-A12, RINm5F, capan-1, capan-2, MIA PaCa-2 (ATCC CRL-1420), PANC-1 (ATCC CRL-1469), AsPC-1 (ATCC CRL-1682), SU-86.86 (ATCC CRL-1837), CFPAC-1 (ATCC CRL-1918), HPAF-II (ATCC CRL-1937), TGP61 (ATCC CRL-2135) and other TGP lines, SW 1990 (ATCC CRL-2172), Mpanc-96 (ATCC CRL-2380), MS1 VEGF  
25 (ATCC CRL-2460), Beta-TC-6 (ATCC CRL-11506), LTPA (ATCC CRL-2389), 266-6 (ATCC CRL-2151), MS1 (ATCC CRL-2779), SVR (ATCC CRL-2280), NIT-2 (ATCC CRL-2364), alphaTC1 Clone 9 (ATCC CRL-2350), ATCC CRL-1492, BxPC-3 (ATCC CRL-1687), HPAC (ATCC CRL-2119), U.S. Pat. Nos. 6,110,743, 5,928,942, 5,888,816, 5,888,705, and 5,723,333, etc., established and primary pancreas cells (e.g., according to  
30 Hellerstrom et al., *Diabetes*, 28:769-76, 1979),

retinal cell lines, RF/6A (CRL 1780), ARPE-19 (CRL-2302), ARPE-19/HPV-16 (CRL-2502), Y79 (HTB-18), WERI-Rb-1 (HTB-169), RPE-J (CRL-2240), SO-Rb50 (retinoblastoma cell line), RBL, HER-Xho1-CC2, WERI-Rb24 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), WERI-Rb27 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), HXO-Rb44, fetal retina cells, retinoblastoma cells, choroidal endothelial cells (e.g., Chor 55), etc., established and primary retinal cells (For other cell lines and methods thereof, see, also, Grieve et al, *Differentiation*, 45:250-7, 1990; Bernstein et al., *Invest. Ophthalmol. Vis. Sci.*, 35:3931-3937, 1994; Howes et al., *Invest. Ophthalmol. Vis. Sci.*, 35:342-351, 1994).

10 Expression control sequences are similarly selected for host compatibility and a desired purpose, e.g., high copy number, high amounts, induction, amplification, controlled expression. Other sequences which can be employed include enhancers such as from SV40, CMV, RSV, inducible promoters, cell-type specific elements, or sequences which allow selective or specific cell expression. Promoters that can be used to drive its expression, 15 include, e.g., the endogenous promoter, MMTV, SV40, trp, lac, tac, or T7 promoters for bacterial hosts; or alpha factor, alcohol oxidase, or PGH promoters for yeast. RNA promoters can be used to produced RNA transcripts, such as T7 or SP6. See, e.g., Melton et al., *Polynucleotide Res.*, 12(18):7035-7056, 1984; Dunn and Studier. *J. Mol. Bio.*, 166:477-435, 1984; U.S. Pat. No. 5,891,636; Studier et al., *Gene Expression Technology, Methods in* 20 *Enzymology*, 85:60-89, 1987. In addition, as discussed above, translational signals (including in-frame insertions) can be included.

When a polynucleotide is expressed as a heterologous gene in a transfected cell line, the gene is introduced into a cell as described above, under effective conditions in which the gene is expressed. The term "heterologous" means that the gene has been introduced into the 25 cell line by the "hand-of-man." Introduction of a gene into a cell line is discussed above. The transfected (or transformed) cell expressing the gene can be lysed or the cell line can be used intact.

For expression and other purposes, a polynucleotide can contain codons found in a naturally-occurring gene, transcript, or cDNA, for example, e.g., as set forth in herein or it 30 can contain degenerate codons coding for the same amino acid sequences. For instance,

it may be desirable to change the codons in the sequence to optimize the sequence for expression in a desired host. See, e.g., U.S. Pat. Nos. 5,567,600 and 5,567,862.

A polypeptide according to the present invention can be recovered from natural sources, transformed host cells (culture medium or cells) according to the usual methods, including, detergent extraction (e.g., non-ionic detergent, Triton X-100, CHAPS, octylglucoside, Igepal CA-630), ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxyapatite chromatography, lectin chromatography, gel electrophoresis. Protein refolding steps can be used, as necessary, in completing the configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for purification steps. Another approach is express the polypeptide recombinantly with an affinity tag (Flag epitope, HA epitope, myc epitope, 6xHis, maltose binding protein, chitinase, etc) and then purify by anti-tag antibody-conjugated affinity chromatography.

The present invention also relates to specific-binding partners. These include antibodies which are specific for polypeptides encoded by polynucleotides of the present invention, as well as other binding-partners which interact with polynucleotides and polypeptides of the present invention. Protein-protein interactions between polypeptides and binding partners can be identified using any suitable methods, e.g., protein binding assays (e.g., filtration assays, chromatography, etc.), yeast two-hybrid system (Fields and Song, *Nature*, 340: 245-247, 1989), protein arrays, gel-shift assays, FRET (fluorescence resonance energy transfer) assays, etc. Nucleic acid interactions (e.g., protein-DNA or protein-RNA) can be assessed using gel-shift assays, e.g., as carried out in U.S. Pat. No. 6,333,407 and 5,789,538.

Antibodies, e.g., polyclonal, monoclonal, recombinant, chimeric, humanized, single-chain, Fab, and fragments thereof, can be prepared according to any desired method. Antibodies, and immune responses, can also be generated by administering naked DNA See, e.g., U.S. Pat. Nos. 5,703,055; 5,589,466; 5,580,859. Antibodies can be used from any source, including, goat, rabbit, mouse, chicken (e.g., IgY; see, Duan, WO/029444 for methods of making antibodies in avian hosts, and harvesting the antibodies from the eggs). An antibody specific for a polypeptide means that the antibody recognizes a defined sequence of

amino acids within or including the polypeptide. Other specific binding partners include, e.g., aptamers and PNA. Antibodies can be prepared against specific epitopes or domains.

Antibodies can also be humanized, e.g., where they are to be used therapeutically. Methods for obtaining human antibodies, e.g., from transgenic mice are described, e.g., in Green et al., Nature Genet. 7:13 (1994); Lonberg et al., Nature 368:856 (1994); and Taylor et al., Int. Immunol. 6:579 (1994). Antibody fragments of the present invention can be prepared by any suitable method, Fab and Fc fragments. single-chain antibodies can also be used. Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest.

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv which are capable of binding to an epitopic determinant present in Bin1 polypeptide. Such antibody fragments retain some ability to selectively bind with its antigen or receptor. The term "epitope" refers to an antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Antibodies can be prepared against specific epitopes or polypeptide domains.

Antibodies which bind to polypeptides of the present invention can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. For example, it may be desirable to produce antibodies that specifically bind to the N- or C-terminal domains of the tissue selective polypeptides of the present invention. The polypeptide or peptide used to immunize an animal which is derived from translated cDNA or chemically synthesized which can be conjugated to a carrier protein, if desired. Such commonly used carriers which are chemically coupled to the immunizing peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid.

Methods of detecting polypeptides



Polypeptides coded for by genes of the present invention can be detected, visualized, determined, quantitated, etc. according to any effective method. useful methods include, e.g., but are not limited to, immunoassays, RIA (radioimmunassay), ELISA, (enzyme-linked-immunosorbent assay), immunoflourescence, flow cytometry, histology, electron microscopy, light microscopy, in situ assays, immunoprecipitation, Western blot, etc.

Immunoassays may be carried in liquid or on biological support. For instance, a sample (e.g., blood, serum, stool, urine, cells, tissue, cerebral spinal fluid, body fluids, etc.) can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support that is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled specific antibody. The solid phase support can then be washed with a buffer a second time to remove unbound antibody. The amount of bound label on solid support may then be detected by conventional means.

A "solid phase support or carrier" includes any support capable of binding an antigen, antibody, or other specific binding partner. Supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, and magnetite. A support material can have any structural or physical configuration. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads

One of the many ways in which gene peptide-specific antibody can be detectably labeled is by linking it to an enzyme and using it in an enzyme immunoassay (EIA). See, e.g., Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)," 1978, Diagnostic Horizons 2, 1-7, Microbiological Associates Quarterly Publication, Walkersville, Md.); Voller, A. et al., 1978, J. Clin. Pathol. 31, 507-520; Butler, J. E., 1981, Meth. Enzymol. 73, 482-523; Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, Fla.. The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety that can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes that can be used to detectably label the antibody include, but are not limited to, malate

dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, .alpha.-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, .beta.-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase,

- 5 glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods that employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays.

- 10 For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect peptides through the use of a radioimmunoassay (RIA). See, e.g., Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

- 15 It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. The antibody can also be detectably  
20 labeled using fluorescence emitting metals such as those in the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

- The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by  
25 detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

- Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological  
30 systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of

luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

#### Diagnostic

5           The present invention also relates to methods and compositions for diagnosing a disorder, or determining susceptibility to a disorder, using polynucleotides, polypeptides, and specific-binding partners of the present invention to detect, assess, determine, etc., a tissue selective gene. In such methods, the gene can serve as a marker for the disorder, e.g., where the gene, when mutant, is a direct cause of the disorder; where the gene is affected by another  
10   gene(s) which is directly responsible for the disorder, e.g., when the gene is part of the same signaling pathway as the directly responsible gene; and, where the gene is chromosomally linked to the gene(s) directly responsible for the disorder, and segregates with it. Many other situations are possible. To detect, assess, determine, etc., a probe specific for the gene can be employed as described above and below. Any method of detecting and/or assessing the gene  
15   can be used, including detecting expression of the gene using polynucleotides, antibodies, or other specific-binding partners.

          The phrase "diagnosing" indicates that it is determined whether the sample has the disorder. A "disorder" means, e.g., any abnormal condition as in a disease or malady. "Determining a subject's susceptibility to a disease or disorder" indicates that the subject is  
20   assessed for whether s/he is predisposed to get such a disease or disorder, where the predisposition is indicated by abnormal expression of the gene (e.g., gene mutation, gene expression pattern is not normal, etc.). Predisposition or susceptibility to a disease may result when a such disease is influenced by epigenetic, environmental, etc., factors. Diagnosing includes prenatal screening where samples from the fetus or embryo (e.g., via amniocentesis  
25   or CV sampling) are analyzed for the expression of the gene.

          By the phrase "assessing expression of a gene or polynucleotide," it is meant that the functional status of the gene is evaluated. This includes, but is not limited to, measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of  
30   polypeptide coded for by said gene. Thus, the term "assessing expression" includes evaluating the all aspects of the transcriptional and translational machinery of the gene. For

instance, if a promoter defect causes, or is suspected of causing, the disorder, then a sample can be evaluated (i.e., "assessed") by looking (e.g., sequencing or restriction mapping) at the promoter sequence in the gene, by detecting transcription products (e.g., RNA), by detecting translation product (e.g., polypeptide). Any measure of whether the gene is functional can be used, including, polypeptide, polynucleotide, and functional assays for the gene's biological activity.

In making the assessment, it can be useful to compare the results to a normal gene, e.g., a gene which is not associated with the disorder. The nature of the comparison can be determined routinely, depending upon how the assessing is accomplished. If, for example, the mRNA levels of a sample is detected, then the mRNA levels of a normal can serve as a comparison, or a gene which is known not to be affected by the disorder. Methods of detecting mRNA are well known, and discussed above, e.g., but not limited to, Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, etc. Similarly, if polypeptide production is used to evaluate the gene, then the polypeptide in a normal tissue sample can be used as a comparison, or, polypeptide from a different gene whose expression is known not to be affected by the disorder. These are only examples of how such a method could be carried out.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions as mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a disease or disease-susceptibility with a gene of the present invention. An association between a disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target. Any region of the gene can be used as a source of the DNA marker, exons, introns, intergenic regions, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the

various individual molecular markers. Maps can be produced for an individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identify the gene

5 responsible for the phenotype. See, e.g., Kruglyak et al., *Am. J. Hum. Genet.*, 58, 1347-1363, 1996; Matise et al., *Nat. Genet.*, 6(4):384-90, 1994.

Assessing the effects of therapeutic and preventative interventions (e.g., administration of a drug, chemotherapy, radiation, etc.) on disorders is a major effort in drug discovery, clinical medicine, and pharmacogenomics. The evaluation of therapeutic and  
10 preventative measures, whether experimental or already in clinical use, has broad applicability, e.g., in clinical trials, for monitoring the status of a patient, for analyzing and assessing animal models, and in any scenario involving disease treatment and prevention. Analyzing the expression profiles of polynucleotides of the present invention can be utilized as a parameter by which interventions are judged and measured. Treatment of a disorder can  
15 change the expression profile in some manner which is prognostic or indicative of the drug's effect on it. Changes in the profile can indicate, e.g., drug toxicity, return to a normal level, etc. Accordingly, the present invention also relates to methods of monitoring or assessing a therapeutic or preventative measure (e.g., chemotherapy, radiation, anti-neoplastic drugs, antibodies, etc.) in a subject having a disorder, or, susceptible to such a disorder, comprising,  
20 e.g., detecting the expression levels of one or more tissue selective genes. A subject can be a cell-based assay system, non-human animal model, human patient, etc. Detecting can be accomplished as described for the methods above and below. By "therapeutic or preventative intervention," it is meant, e.g., a drug administered to a patient, surgery, radiation, chemotherapy, and other measures taken to prevent, treat, or diagnose a disorder.

25 The present invention also relates to methods of using binding partners, such as antibodies, to deliver active agents to the tissue (e.g., kidney or pancreas or an immune cells) for a variety of different purposes, including, e.g., for diagnostic, therapeutic, and research purposes. Methods can involve delivering or administering an active agent to the tissue, comprising, e.g., administering to a subject in need thereof, an effective amount of an active  
30 agent coupled to a binding partner specific for a tissue selective polypeptide, wherein said binding partner is effective to deliver said active agent specifically to the target tissue.

Any type of active agent can be used in combination with it, including, therapeutic, cytotoxic, cytostatic, chemotherapeutic, anti-neoplastic, anti-proliferative, anti-biotic, etc., agents. A chemotherapeutic agent can be, e.g., DNA-interactive agent, alkylating agent, antimetabolite, tubulin-interactive agent, hormonal agent, hydroxyurea, Cisplatin,

- 5 Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, paclitaxel, cytoxan, 2-methoxy-carbonyl-amino-benzimidazole, Plicamycin, Methotrexate, Fluorouracil, Fluorodeoxyuridin, CB3717, Azacitidine, Floxuridine, Mercaptopurine, 6-Thioguanine, Pentostatin, Cytarabine, Fludarabine, etc. Agents can also be contrast agents useful in imaging technology, e.g., X-ray, CT, CAT, MRI, ultrasound,
- 10 PET, SPECT, and scintographic.

- An active agent can be associated in any manner with a binding partner which is effective to achieve its delivery specifically to the target. Specific delivery or targeting indicates that the agent is provided to the tissue, without being substantially provided to other tissues. This is useful especially where an agent is toxic, and specific targeting to the tissue
- 15 enables the majority of the toxicity to be aimed at the tissue, with as small as possible effect on other tissues in the body. The association of the active agent and the binding partner ("coupling") can be direct, e.g., through chemical bonds between the binding partner and the agent, or, via a linking agent, or the association can be less direct, e.g., where the active agent is in a liposome, or other carrier, and the binding partner is associated with the liposome
- 20 surface. In such case, the binding partner can be oriented in such a way that it is able to bind to tissue selective polypeptide, e.g., exposed on the cell surface. Methods for delivery of DNA via a cell-surface receptor is described, e.g., in U.S. Pat. No. 6,339,139.

#### Identifying agent methods

- 25 The present invention also relates to methods of identifying agents, and the agents themselves, which modulate tissue selective genes. These agents can be used to modulate the biological activity of the polypeptide encoded for the gene, or the gene, itself. Agents which regulate the gene or its product are useful in variety of different environments, including as medicinal agents to treat or prevent disorders associated with genes and as research reagents
- 30 to modify the function of tissues and cell.

Methods of identifying agents generally comprise steps in which an agent is placed in contact with the gene, its transcription product, its translation product, or other target, and then a determination is performed to assess whether the agent "modulates" the target. The specific method utilized will depend upon a number of factors, including, e.g., the target (i.e.,  
5 is it the gene or polypeptide encoded by it), the environment (e.g., *in vitro* or *in vivo*), the composition of the agent, etc.

For modulating the expression of tissue selective genes, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a gene (e.g., in a cell population) with a test agent under conditions effective for said test agent to modulate the  
10 expression of tissue selective genes, and determining whether said test agent modulates said genes. An agent can modulate expression of a tissue selective gene at any level, including transcription (e.g., by modulating the promoter), translation, and/or perdurance of the nucleic acid (e.g., degradation, stability, etc.) in the cell.

For modulating the biological activity of polypeptides, a method can comprise, in any  
15 effective order, one or more of the following steps, e.g., contacting a polypeptide (e.g., in a cell, lysate, or isolated) with a test agent under conditions effective for said test agent to modulate the biological activity of said polypeptide, and determining whether said test agent modulates said biological activity.

Contacting a gene or polypeptide with the test agent can be accomplished by any  
20 suitable method and/or means that places the agent in a position to functionally control expression or biological activity. Functional control indicates that the agent can exert its physiological effect through whatever mechanism it works. The choice of the method and/or means can depend upon the nature of the agent and the condition and type of environment in which the gene or polypeptide is presented, e.g., lysate, isolated, or in a cell population (such  
25 as, *in vivo*, *in vitro*, organ explants, etc.). For instance, if the cell population is an *in vitro* cell culture, the agent can be contacted with the cells by adding it directly into the culture medium. If the agent cannot dissolve readily in an aqueous medium, it can be incorporated into liposomes, or another lipophilic carrier, and then administered to the cell culture. Contact can also be facilitated by incorporation of agent with carriers and delivery molecules  
30 and complexes, by injection, by infusion, etc.

Agents can be directed to, or targeted to, any part of the polypeptide which is

effective for modulating it. For example, agents, such as antibodies and small molecules, can be targeted to cell-surface, exposed, extracellular, ligand binding, functional, etc., domains of the polypeptide. Agents can also be directed to intracellular regions and domains, e.g., regions where the polypeptide couples or interacts with intracellular or intramembrane binding partners.

After the agent has been administered in such a way that it can gain access, it can be determined whether the test agent modulates expression or biological activity. Modulation can be of any type, quality, or quantity, e.g., increase, facilitate, enhance, up-regulate, stimulate, activate, amplify, augment, induce, decrease, down-regulate, diminish, lessen, reduce, etc. The modulatory quantity can also encompass any value, e.g., 1%, 5%, 10%, 50%, 75%, 1-fold, 2-fold, 5-fold, 10-fold, 100-fold, etc. To modulate expression means, e.g., that the test agent has an effect on its expression, e.g., to effect the amount of transcription, to effect RNA splicing, to effect translation of the RNA into polypeptide, to effect RNA or polypeptide stability, to effect polyadenylation or other processing of the RNA, to effect post-transcriptional or post-translational processing, etc. To modulate biological activity means, e.g., that a functional activity of the polypeptide is changed in comparison to its normal activity in the absence of the agent. This effect includes, increase, decrease, block, inhibit, enhance, etc.

A test agent can be of any molecular composition, e.g., chemical compounds, biomolecules, such as polypeptides, lipids, nucleic acids (e.g., antisense), carbohydrates, antibodies, ribozymes, double-stranded RNA, aptamers, etc. For example, if a polypeptide to be modulated is a cell-surface molecule, a test agent can be an antibody that specifically recognizes it and, e.g., causes the polypeptide to be internalized, leading to its down regulation on the surface of the cell. Such an effect does not have to be permanent, but can require the presence of the antibody to continue the down-regulatory effect. Antibodies can also be used to modulate the biological activity of a polypeptide in a lysate or other cell-free form.

Additional cell-based test systems suitable for the analysis of GPCR polypeptides are summarized in Marchese et al. (1999, Trends in Pharmacol. Sci. 20: 370-375) and comprise so-called "ligand screening assays." For example in yeast cells the pheromon receptor can be replaced by a GPCR according to the invention. The effect of test substances on the receptor



can be determined upon modulation of histidine synthesis, i.e. by growing in histidine-free medium. In addition using cells transfected with nucleic acids according to the invention it can be analyzed whether test substances mediate translocation of a detectable arrestins, for example of a arrestin-GFP-fusion protein. Moreover, it can be analyzed whether test

5 substances mediate GPCR-mediated dispersion or aggregation of *Xenopus laevis* melanophores. Another test system utilizes the universal adapter G-protein G  $\alpha_{\text{phal6}}$ , which mobilizes  $\text{Ca}_{\text{sup.2+}}$ . Other screening test systems are described in Lemer et al., supra; WO96/41169; U.S. Pat. No. 5,482,835; WO99/06535; EP 0 939 902; WO99/66326; WO98/34948; EP 0 863 214; U.S. Pat. No. 5,882,944 and U.S. Pat. No. 5,891,641.

## 10 Therapeutics

Selective polynucleotides, polypeptides, and specific-binding partners thereto, can be utilized in therapeutic applications, especially to treat diseases and conditions described herein. Useful methods include, but are not limited to, immunotherapy (e.g., using specific-binding partners to polypeptides), vaccination (e.g., using a selective polypeptide or a naked

15 DNA encoding such polypeptide), protein or polypeptide replacement therapy, gene therapy (e.g., germ-line correction, antisense), etc.

Various immunotherapeutic approaches can be used. For instance, unlabeled antibody that specifically recognizes a tissue-specific antigen can be used to stimulate the body to destroy or attack a cancer or other diseased tissue, to cause down-regulation, to

20 produce complement-mediated lysis, to inhibit cell growth, etc., of target cells which display the antigen, e.g., analogously to how c-erbB-2 antibodies are used to treat breast cancer. In addition, antibody can be labeled or conjugated to enhance its deleterious effect, e.g., with radionuclides and other energy emitting entities, toxins, such as ricin, exotoxin A (ETA), and diphtheria, cytotoxic or cytostatic agents, immunomodulators, chemotherapeutic agents;

25 etc. See, e.g., U.S. Pat. No. 6,107,090.

An antibody or other specific-binding partner can be conjugated to a second molecule, such as a cytotoxic agent, and used for targeting the second molecule to a tissue-antigen positive cell (Vitetta, E. S. et al., 1993, Immunotoxin therapy, in DeVita, Jr., V. T. et al., eds, Cancer: Principles and Practice of Oncology, 4th ed., J. B. Lippincott Co., Philadelphia,

30 2624-2636). Examples of cytotoxic agents include, but are not limited to, antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, radioisotopes and

chemotherapeutic agents. Further examples of cytotoxic agents include, but are not limited to ricin, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, 1-dehydrotestosterone, diphtheria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin, elongation factor-2 and glucocorticoid. Techniques for conjugating therapeutic agents to antibodies are well.

In addition to immunotherapy, polynucleotides and polypeptides can be used as targets for non-immunotherapeutic applications, e.g., using compounds which interfere with function, expression (e.g., antisense as a therapeutic agent), assembly, etc. RNA interference can be used in vitro and in vivo to silence a gene when its expression contributes to a disease (but also for other purposes, e.g., to identify the gene's function to change a developmental pathway of a cell, etc.). See, e.g., Sharp and Zamore, *Science*, 287:2431-2433, 2001; Grishok et al., *Science*, 287:2494, 2001.

Delivery of therapeutic agents can be achieved according to any effective method, including, liposomes, viruses, plasmid vectors, bacterial delivery systems, orally, systemically, etc. Therapeutic agents of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch), intravenously, ophthalmic, nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

In addition to therapeutics, *per se*, the present invention also relates to methods of treating a disease showing altered expression of a tissue selective gene, comprising, e.g., administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of said gene and/or which is effective in treating said disease. The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder. By the phrase "altered expression," it is meant that the disease is associated with a mutation in the gene, or any modification to the gene (or corresponding product) which affects its normal function. Thus, expression refers to, e.g., transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential

expression, etc.

Any agent which "treats" the disease can be used. Such an agent can be one which regulates the expression of a tissue selective gene. Expression refers to the same acts already mentioned, e.g. transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential expression, etc. For instance, if the condition was a result of a complete deficiency of the gene product, administration of gene product to a patient would be said to treat the disease and regulate the gene's expression. Many other possible situations are possible, e.g., where the gene is aberrantly expressed, and the therapeutic agent regulates the aberrant expression by restoring its normal expression pattern.

#### Antisense

Antisense polynucleotide (e.g., RNA) can also be prepared from a polynucleotide according to the present invention. Antisense polynucleotide can be used in various ways, such as to regulate or modulate expression of the polypeptides they encode, e.g., inhibit their expression, for in situ hybridization, for therapeutic purposes, for making targeted mutations (in vivo, triplex, etc.) etc. For guidance on administering and designing anti-sense, see, e.g., U.S. Pat. Nos. 6,200,960, 6,200,807, 6,197,584, 6,190,869, 6,190,661, 6,187,587, 6,168,950, 6,153,595, 6,150,162, 6,133,246, 6,117,847, 6,096,722, 6,087,343, 6,040,296, 6,005,095, 5,998,383, 5,994,230, 5,891,725, 5,885,970, and 5,840,708. An antisense polynucleotides can be operably linked to an expression control sequence. A total length of about 35 bp can be used in cell culture with cationic liposomes to facilitate cellular uptake, but for *in vivo* use, preferably shorter oligonucleotides are administered, e.g. 25 nucleotides.

Antisense polynucleotides can comprise modified, nonnaturally-occurring nucleotides and linkages between the nucleotides (e.g., modification of the phosphate-sugar backbone; methyl phosphonate, phosphorothioate, or phosphorodithioate linkages; and 2'-O-methyl ribose sugar units), e.g., to enhance in vivo or in vitro stability, to confer nuclease resistance, to modulate uptake, to modulate cellular distribution and compartmentalization, etc. Any effective nucleotide or modification can be used, including those already mentioned, as known in the art, etc., e.g., disclosed in U.S. Pat. Nos. 6,133,438; 6,127,533; 6,124,445; 6,121,437; 5,218,103 (e.g., nucleoside thiophosphoramidites); 4,973,679; Sproat et al., "2'-O-Methyloligoribonucleotides: synthesis and applications," Oligonucleotides and Analogs A

Practical Approach, Eckstein (ed.), IRL Press, Oxford, 1991, 49-86; Iribarren et al., "2'-O-Alkyl Oligoribonucleotides as Antisense Probes," Proc. Natl. Acad. Sci. USA, 1990, 87, 7747-7751; Cotton et al., "2'-O-methyl, 2'-O-ethyl oligoribonucleotides and phosphorothioate oligodeoxyribonucleotides as inhibitors of the in vitro U7 snRNP-dependent mRNA

5 processing event," Nucl. Acids Res., 1991, 19, 2629-2635.

#### Arrays

The present invention also relates to an ordered array of polynucleotide probes and specific-binding partners (e.g., antibodies) for detecting the expression of tissue selective  
10 genes or polypeptides encoded thereby, in a sample, comprising, one or more polynucleotide probes or specific binding partners associated with a solid support or in separate receptacles, wherein each probe is specific for a tissue selective gene or a specific-binding partner which is specific for a polypeptide.

The phrase "ordered array" indicates that the probes are arranged in an identifiable or  
15 position-addressable pattern, e.g., such as the arrays disclosed in U.S. Pat. Nos. 6,156,501, 6,077,673, 6,054,270, 5,723,320, 5,700,637, WO09919711, WO00023803. The probes are associated with the solid support in any effective way. For instance, the probes can be bound to the solid support, either by polymerizing the probes on the substrate, or by attaching a probe to the substrate. Association can be, covalent, electrostatic, noncovalent, hydrophobic,  
20 hydrophilic, noncovalent, coordination, adsorbed, absorbed, polar, etc. When fibers or hollow filaments are utilized for the array, the probes can fill the hollow orifice, be absorbed into the solid filament, be attached to the surface of the orifice, etc. Probes can be of any effective size, sequence identity, composition, etc., as already discussed.

#### 25 Transgenic animals

The present invention also relates to transgenic animals comprising tissue selective genes, and homologs thereof. (Methods of making transgenic animals, and associated recombinant technology, can be accomplished conventionally, e.g., as described in *Transgenic Animal Technology*, Pinkert et al., 2<sup>nd</sup> Edition, Academic Press, 2002.) Such  
30 genes, as discussed in more detail below, include, but are not limited to, functionally-disrupted genes, mutated genes, ectopically or selectively-expressed genes, inducible or

regulatable genes, etc. These transgenic animals can be produced according to any suitable technique or method, including homologous recombination, mutagenesis (e.g., ENU, Rathkolb et al., *Exp. Physiol.*, 85(6):635-644, 2000), and the tetracycline-regulated gene expression system (e.g., U.S. Pat. No. 6,242,667). The term "gene" as used herein includes  
5 any part of a gene, i.e., regulatory sequences, promoters, enhancers, exons, introns, coding sequences, etc. The nucleic acid present in the construct or transgene can be naturally-occurring wild-type, polymorphic, or mutated. Where the animal is a non-human animal, its homolog can be used instead. Transgenic animals can have structural and/or functional defects in any of the tissues described herein, e.g., pancreas, kidney, retina, and immune cells,  
10 as well as having or being susceptible to any of the associated disorders or diseases mentioned herein.

Along these lines, polynucleotides of the present invention can be used to create transgenic animals, e.g. a non-human animal, comprising at least one cell whose genome comprises a functional disruption of one or tissue selective genes, or homologs thereof (e.g.,  
15 a mouse homolog when a mouse is used). By the phrases "functional disruption" or "functionally disrupted," it is meant that the gene does not express a biologically-active product. It can be substantially deficient in at least one functional activity coded for by the gene. Expression of a polypeptide can be substantially absent, i.e., essentially undetectable amounts are made. However, polypeptide can also be made, but which is deficient in  
20 activity, e.g., where only an amino-terminal portion of the gene product is produced.

The transgenic animal can comprise one or more cells. When substantially all its cells contain the engineered gene, it can be referred to as a transgenic animal "whose genome comprises" the engineered gene. This indicates that the endogenous gene loci of the animal has been modified and substantially all cells contain such modification.

25 Functional disruption of the gene can be accomplished in any effective way, including, e.g., introduction of a stop codon into any part of the coding sequence such that the resulting polypeptide is biologically inactive (e.g., because it lacks a catalytic domain, a ligand binding domain, etc.), introduction of a mutation into a promoter or other regulatory sequence that is effective to turn it off, or reduce transcription of the gene, insertion of an  
30 exogenous sequence into the gene which inactivates it (e.g., which disrupts the production of a biologically-active polypeptide or which disrupts the promoter or other transcriptional

machinery), deletion of sequences from the gene (or homolog thereof), etc. Examples of transgenic animals having functionally disrupted genes are well known, e.g., as described in U.S. Pat. Nos. 6,239,326, 6,225,525, 6,207,878, 6,194,633, 6,187,992, 6,180,849, 6,177,610, 6,100,445, 6,087,555, 6,080,910, 6,069,297, 6,060,642, 6,028,244, 6,013,858, 5,981,830, 5,866,760, 5,859,314, 5,850,004, 5,817,912, 5,789,654, 5,777,195, and 5,569,824. A transgenic animal which comprises the functional disruption can also be referred to as a "knock-out" animal, since the biological activity of its gene has been "knocked-out." Knock-outs can be homozygous or heterozygous.

For creating functionally disrupted genes, and other gene mutations, homologous recombination technology is of special interest since it allows specific regions of the genome to be targeted. Using homologous recombination methods, genes can be specifically-inactivated, specific mutations can be introduced, and exogenous sequences can be introduced at specific sites. These methods are well known in the art, e.g., as described in the patents above. See, also, Robertson, *Biol. Reproduc.*, 44(2):238-245, 1991. Generally, the genetic engineering is performed in an embryonic stem (ES) cell, or other pluripotent cell line (e.g., adult stem cells, EG cells), and that genetically-modified cell (or nucleus) is used to create a whole organism. Nuclear transfer can be used in combination with homologous recombination technologies. For example, a gene locus can be disrupted in mouse ES cells using a positive-negative selection method (e.g., Mansour et al., *Nature*, 336:348-352, 1988). In this method, a targeting vector can be constructed which comprises a part of the gene to be targeted. A selectable marker, such as neomycin resistance genes, can be inserted into an exon present in the targeting vector, disrupting it. When the vector recombines with the ES cell genome, it disrupts the function of the gene. The presence in the cell of the vector can be determined by expression of neomycin resistance. See, e.g., U.S. Pat. No. 6,239,326. Cells having at least one functionally disrupted gene can be used to make chimeric and germline animals, e.g., animals having somatic and/or germ cells comprising the engineered gene. Homozygous knock-out animals can be obtained from breeding heterozygous knock-out animals. See, e.g., U.S. Pat. No. 6,225,525.

The present invention also relates to non-human, transgenic animal whose genome comprises recombinant tissue selective nucleic acid (and homologs thereof) operatively linked to an expression control sequence effective to express said coding sequence in a target

tissue. Such a transgenic animal can also be referred to as a "knock-in" animal since an exogenous gene has been introduced, stably, into its genome. "Operable linkage" has the meaning used through the specification, i.e., placed in a functional relationship with another nucleic acid. When a gene is operably linked to an expression control sequence, as explained  
5 above, it indicates that the gene (e.g., coding sequence) is joined to the expression control sequence (e.g., promoter) in such a way that facilitates transcription and translation of the coding sequence. As described above, the phrase "genome" indicates that the genome of the cell has been modified. In this case, the recombinant gene has been stably integrated into the genome of the animal. The nucleic acid (e.g., a coding sequence) in operable linkage with  
10 the expression control sequence can also be referred to as a construct or transgene.

Any expression control sequence can be used depending on the purpose. For instance, if selective expression is desired, then expression control sequences which limit its expression can be selected. These include, e.g., tissue or cell-specific promoters, introns, enhancers, etc. For various methods of cell and tissue-specific expression, see, e.g., U.S. Pat.  
15 Nos. 6,215,040, 6,210,736, and 6,153,427. These also include the endogenous promoter, i.e., the coding sequence can be operably linked to its own promoter. Inducible and regulatable promoters can also be utilized.

The present invention also relates to a transgenic animal which contains a functionally disrupted and a transgene stably integrated into the animals genome. Such an animal can be  
20 constructed using combinations any of the above- and below-mentioned methods. Such animals have any of the aforementioned uses, including permitting the knock-out of the normal gene and its replacement with a mutated gene. Such a transgene can be integrated at the endogenous gene locus so that the functional disruption and "knock-in" are carried out in the same step.

25 In addition to the methods mentioned above, transgenic animals can be prepared according to known methods, including, e.g., by pronuclear injection of recombinant genes into pronuclei of 1-cell embryos, incorporating an artificial yeast chromosome into embryonic stem cells, gene targeting methods, embryonic stem cell methodology, cloning methods, nuclear transfer methods. See, also, e.g., U.S. Patent Nos. 4,736,866; 4,873,191;  
30 4,873,316; 5,082,779; 5,304,489; 5,174,986; 5,175,384; 5,175,385; 5,221,778; Gordon et al., Proc. Natl. Acad. Sci., 77:7380-7384, 1980; Palmiter et al., Cell, 41:343-345, 1985; Palmiter

et al., *Ann. Rev. Genet.*, 20:465-499, 1986; Askew et al., *Mol. Cell. Bio.*, 13:4115-4124, 1993; Games et al. *Nature*, 373:523-527, 1995; Valancius and Smithies, *Mol. Cell. Bio.*, 11:1402-1408, 1991; Stacey et al., *Mol. Cell. Bio.*, 14:1009-1016, 1994; Hasty et al., *Nature*, 350:243-246, 1995; Rubinstein et al., *Nucl. Acid Res.*, 21:2613-2617, 1993; Cibelli et al.,  
5 *Science*, 280:1256-1258, 1998. For guidance on recombinase excision systems, see, e.g., U.S. Pat. Nos. 5,626,159, 5,527,695, and 5,434,066. See also, Orban, P.C., et al., "Tissue- and Site-Specific DNA Recombination in Transgenic Mice," *Proc. Natl. Acad. Sci. USA*, 89:6861-6865 (1992); O'Gorman, S., et al., "Recombinase-Mediated Gene Activation and Site-Specific Integration in Mammalian Cells," *Science*, 251:1351-1355 (1991); Sauer, B., et  
10 al., "Cre-stimulated recombination at loxP-Containing DNA sequences placed into the mammalian genome," *Polynucleotides Research*, 17(1):147-161 (1989); Gagneten, S. et al. (1997) *Nucl. Acids Res.* 25:3326-3331; Xiao and Weaver (1997) *Nucl. Acids Res.* 25:2985-2991; Agah, R. et al. (1997) *J. Clin. Invest.* 100:169-179; Barlow, C. et al. (1997) *Nucl. Acids Res.* 25:2543-2545; Araki, K. et al. (1997) *Nucl. Acids Res.* 25:868-872; Mortensen,  
15 R. N. et al. (1992) *Mol. Cell. Biol.* 12:2391-2395 (G418 escalation method); Lakhiani, P. P. et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:9950-9955 ("hit and run"); Westphal and Leder (1997) *Curr. Biol.* 7:530-533 (transposon-generated "knock-out" and "knock-in"); Templeton, N. S. et al. (1997) *Gene Ther.* 4:700-709 (methods for efficient gene targeting, allowing for a high frequency of homologous recombination events, e.g., without selectable  
20 markers); PCT International Publication WO 93/22443 (functionally-disrupted).

A polynucleotide according to the present invention can be introduced into any non-human animal, including a non-human mammal, mouse (Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1986), pig (Hammer et al., *Nature*, 315:343-345, 1985), sheep (Hammer et al.,  
25 *Nature*, 315:343-345, 1985), cattle, rat, or primate. See also, e.g., Church, 1987, *Trends in Biotech.* 5:13-19; Clark et al., *Trends in Biotech.* 5:20-24, 1987); and DePamphilis et al., *BioTechniques*, 6:662-680, 1988. Transgenic animals can be produced by the methods described in U.S. Pat. No. 5,994,618, and utilized for any of the utilities described therein.

### 30 Database

The present invention also relates to electronic forms of polynucleotides,



polypeptides, etc., of the present invention, including computer-readable medium (e.g., magnetic, optical, etc., stored in any suitable format, such as flat files or hierarchical files) which comprise such sequences, or fragments thereof, e-commerce-related means, etc.

Along these lines, the present invention relates to methods of retrieving nucleic acid and/or

- 5 polypeptide sequences from a computer-readable medium, comprising, one or more of the following steps in any effective order, e.g., selecting a cell or gene expression profile, e.g., a profile that specifies that said gene is differentially expressed in a tissue as described herein, and retrieving said differentially expressed nucleic acid or polypeptide.

- A "gene expression profile" means the list of tissues, cells, etc., in which a defined  
10 gene is expressed (i.e., transcribed and/or translated). A "cell expression profile" means the genes which are expressed in the particular cell type. The profile can be a list of the tissues in which the gene is expressed, but can include additional information as well, including level of expression (e.g., a quantity as compared or normalized to a control gene), and information on temporal (e.g., at what point in the cell-cycle or developmental program) and  
15 spatial expression. By the phrase "selecting a gene or cell expression profile," it is meant that a user decides what type of gene or cell expression pattern he is interested in retrieving, e.g., he may require that the gene is differentially expressed in a tissue, or he may require that the gene is not expressed in blood, but must be expressed in pancreas. Any pattern of expression preferences may be selected. The selecting can be performed by any effective method. In  
20 general, "selecting" refers to the process in which a user forms a query that is used to search a database of gene expression profiles. The step of retrieving involves searching for results in a database that correspond to the query set forth in the selecting step. Any suitable algorithm can be utilized to perform the search query, including algorithms that look for matches, or that perform optimization between query and data. The database is information that has been  
25 stored in an appropriate storage medium, having a suitable computer-readable format. Once results are retrieved, they can be displayed in any suitable format, such as HTML.

- For instance, the user may be interested in identifying genes that are differentially expressed in a pancreas or kidney. He may not care whether small amounts of expression occur in other tissues, as long as such genes are not expressed in peripheral blood  
30 lymphocytes. A query is formed by the user to retrieve the set of genes from the database

having the desired gene or cell expression profile. Once the query is inputted into the system, a search algorithm is used to interrogate the database, and retrieve results.

#### Advertising, licensing, etc., methods

5           The present invention also relates to methods of advertising, licensing, selling, purchasing, brokering, etc., genes, polynucleotides, specific-binding partners, antibodies, etc., of the present invention. Methods can comprises, e.g., displaying tissue selective polynucleotide or polypeptide sequences, or antibody specific thereto, in a printed or computer-readable medium (e.g., on the Web or Internet), accepting an offer to purchase said  
10   gene, polypeptide, or antibody.

#### Other

          A polynucleotide, probe, polypeptide, antibody, specific-binding partner, etc., according to the present invention can be isolated. The term "isolated" means that the  
15   material is in a form in which it is not found in its original environment or in nature, e.g., more concentrated, more purified, separated from component, etc. An isolated polynucleotide includes, e.g., a polynucleotide having the sequenced separated from the chromosomal DNA found in a living animal, e.g., as the complete gene, a transcript, or a cDNA. This polynucleotide can be part of a vector or inserted into a chromosome (by  
20   specific gene-targeting or by random integration at a position other than its normal position) and still be isolated in that it is not in a form that is found in its natural environment. A polynucleotide, polypeptide, etc., of the present invention can also be substantially purified. By substantially purified, it is meant that polynucleotide or polypeptide is separated and is essentially free from other polynucleotides or polypeptides, i.e., the polynucleotide or  
25   polypeptide is the primary and active constituent. A polynucleotide can also be a recombinant molecule. By "recombinant," it is meant that the polynucleotide is an arrangement or form which does not occur in nature. For instance, a recombinant molecule comprising a promoter sequence would not encompass the naturally-occurring gene, but would include the promoter operably linked to a coding sequence not associated with it in  
30   nature, e.g., a reporter gene, or a truncation of the normal coding sequence.

The term "marker" is used herein to indicate a means for detecting or labeling a target. A marker can be a polynucleotide (usually referred to as a "probe"), polypeptide (e.g., an antibody conjugated to a detectable label), PNA, or any effective material.

The topic headings set forth above are meant as guidance where certain information  
5 can be found in the application, but are not intended to be the only source in the application where information on such topic can be found. Reference materials

For other aspects of the polynucleotides, reference is made to standard textbooks of molecular biology. See, e.g., Hames et al., Polynucleotide Hybridization, IL Press, 1985; Davis et al., Basic Methods in Molecular Biology, Elsevir Sciences Publishing, Inc., New  
10 York, 1986; Sambrook et al., Molecular Cloning, CSH Press, 1989; Howe, Gene Cloning and Manipulation, Cambridge University Press, 1995; Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., 1994-1998.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following  
15 preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated by reference in their entirety, including U.S. Application Serial Nos. 60/372,669 April 16, 2003, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366  
20 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002.

TABLE 1

Clone ID (gene code)	ACCN	Predominant sites of expression	Other expression sites	Cytogenetic locus
TMD0024	XM_060945	thymus	none	1q22
TMD1779	XM_060946	thymus and PBL	none	1q22
TMD0884	XM_060947	thymus	skin and ovary	1q22
TMD0025	XM_060948	thymus	none	1q22
TMD1780	XM_089422	thymus	none	1q22
TMD1781	XM_089421	PBL	thymus	1q22
TMD0304	XM_060956	bone marrow and muscle	testis	1q22
TMD0888	XM_060957	bone marrow	lung, muscle and testis	1q22
TMD0890	XM_060959	bone marrow	lung and PBL	1q22

TABLE 2

Clone ID (gene code)	ACCN	Protein seq length	Domain Description
TMD1779	XM_060946	264	Transmembrane domain: 26 - 48 Transmembrane domain: 55 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 134 - 156 Transmembrane domain: 197 - 219
TMD0024	XM_060945	268	Transmembrane domain: 16 - 38 Transmembrane domain: 53 - 75 Transmembrane domain: 96 - 118 Transmembrane domain: 156 - 178 Transmembrane domain: 191 - 213 Transmembrane domain: 228 - 246
TMD0025	XM_060948	313	Transmembrane domain: 29 - 51 Transmembrane domain: 58 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 135 - 157 Transmembrane domain: 197 - 219 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0304	XM_060956	319	Transmembrane domain: 28 - 50 Transmembrane domain: 63 - 82 Transmembrane domain: 102 - 124 Transmembrane domain: 144 - 166 Transmembrane domain: 205 - 227 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0884	XM_060947	299	Transmembrane domain: 20 - 42 Transmembrane domain: 54 - 76 Transmembrane domain: 91 - 113 Transmembrane domain: 126 - 148

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				Transmembrane domain: 183 - 205
				Transmembrane domain: 226 - 248
				Transmembrane domain: 258 - 277
5	TMD0888	XM_060957	312	Transmembrane domain: 25 - 47
				Transmembrane domain: 59 - 78
				Transmembrane domain: 98 - 120
				Transmembrane domain: 141 - 163
10				Transmembrane domain: 207 - 229
				Transmembrane domain: 241 - 260
				Transmembrane domain: 270 - 292
	TMD0890	XM_060959	280	Transmembrane domain: 26 - 48
15				Transmembrane domain: 122 - 144
				Transmembrane domain: 180 - 202
				Transmembrane domain: 215 - 237
				Transmembrane domain: 252 - 269
20	TMD1780	XM_089422	491	Transmembrane domain: 20 - 42
				Transmembrane domain: 54 - 76
				Transmembrane domain: 91 - 113
				Transmembrane domain: 137 - 159
				Transmembrane domain: 190 - 212
25				Transmembrane domain: 231 - 253
				Transmembrane domain: 266 - 283
				Transmembrane domain: 304 - 326
				Transmembrane domain: 336 - 358
				Transmembrane domain: 379 - 401
30				Transmembrane domain: 437 - 459
	TMD1781	XM_089421	491	Transmembrane domain: 63 - 85
35				

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	TMD0024 XM_060945	TMD1779 XM_060946	TMD0884 XM_060947	TMD0025 XM_060948	TMD1780 XM_089422	TMD1781 XM_089421	TMD0304 XM_060956	TMD0888 XM_060957
TMD0024 XM_060945								
TMD1779 XM_060946	no significant similarity							
TMD0884 XM_060947	74%(371nt)	no significant similarity						
TMD0025 XM_060948	71%(222nt) 80%(73nt)	90%(605nt)	83%(54nt)					
TMD1780 XM_089422	81%(114nt) 74%(186nt) 79%(113nt) 77%(99nt)	83%(71nt)	78%(90nt)	80%(84nt)				
TMD1781 XM_089421	91%(35nt) 77%(80nt)	no significant similarity	no significant similarity	no significant similarity	77%(179nt) 82%(46nt)			
TMD0304 XM_060956	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)	no significant similarity		
TMD0888 XM_060957	no significant similarity	no significant similarity	no significant similarity	84%(38nt)	no significant similarity	no significant similarity	73%(241nt)	
TMD0890 XM_060959	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)

TABLE 3

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	TMD0024 XP_060945	TMD1779 XP_060946	TMD0884 XP_060947	TMD0025 XP_060948	TMD1780 XP_089422	TMD1781 XP_089421	TMD0304 XP_060956	TMD0888 XP_060957
TMD0024 XP_060945								
TMD1779 XP_060946	47%(200aa)							
TMD0884 XP_060947	62%(171aa)	36%(92aa)						
TMD0025 XP_060948	53%(252aa)	73%(233aa)	46%(166aa)					
TMD1780 XP_089422	59%(261aa) 59%(181aa)	46%(227aa) 46%(169aa)	55%(165aa) 47%(111aa)	52%(300aa)				
TMD1781 XP_089421	40%(94aa)	35%(82aa)	52%(40aa)	37%(94aa)	51%(93aa) 49%(77aa)			
TMD0304 XP_060956	40%(257aa)	37%(229aa)	36%(163aa)	39%(299aa)	39%(300aa)	34%(89aa)		
TMD0888 XP_060957	49%(251aa)	37%(239aa)	41%(157aa)	40%(305aa)	45%(304aa) 43%(189aa)	41%(82aa)	50%(301aa)	
TMD0890 XP_060959	41%(196)	32%(132aa)	32%(156aa)	36%(179aa)	42%(200aa)	38%(72aa)	36%(196aa)	46%(196aa)

TABLE 4





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TABLE 5

CLONE ID	FOUR	FOUR	PROMOTER
TMD1779 (SEQ ID NO 1-2)	GGTCAATGAGACTGTGG (SEQ ID NO 3)	CTATCAGTCCAGTGTGGAA GGAAACTGAAG (SEQ ID NO 4)	CTCTTCAGATTAAATGGCCAGACCTAGTTTATGGTGCAGACATT (SEQ ID NO 5)
TMD0024 (SEQ ID NO 6-7)	CCAGCTGCTCTGAGACA CCAAGACC (SEQ ID NO 8)	GGCACCATAATTACCAGGAT GCTGAGG (SEQ ID NO 9)	GAGTGGCAATATATAAGAGGTAATGTTCAATGCAACATGTTAAATGCAA (SEQ ID NO 10) ACTCCTTAGATAAAAGGGCAGATTATTAAGAACCCCTGATTAAATCA (SEQ ID NO 11)
TMD0025 (SEQ ID NO 12-13)	CCTGTTCACTCTGGGCA CCAATGC (SEQ ID NO 14)	CTGGTGGAGGAGTGGAG GGCAG (SEQ ID NO 15)	TAATCTATGTAAAAATCCACTGGAGTAGAAATCAGCTGCTCTCATGTGCC (SEQ ID NO 16) TACCTTCTGTATATAAAACATATACTAATAACACACACTCATACAC (SEQ ID NO 17) CTTCAGAGGTATATAATGAAGACTGGATACCAAGACACTACTGGATG (SEQ ID NO 18) CCCTGGAGATATAAAAGTTCCAGTAAATAGATGTGTGCTCAGCATCTT (SEQ ID NO 19)
TMD0304 (SEQ ID NO 20-21)	CTCTATGTTCCGCGATGC GCACAG (SEQ ID NO 22)	GCAAGGTGGAAATCCATGCA ATCTCAG (SEQ ID NO 23)	AGACAGAGTTAAAAATGACCAAACTACAGAAAAATATTTCCAGATAAT (SEQ ID NO 24)
TMD0884 (SEQ ID NO 25-26)	TGTCAATATCTCTGGTGT CAGTGTGCTCC (SEQ ID NO 27)	CATCTACCCAGAACCTTTCT CAGAGCCATC (SEQ ID NO 28)	GTCACGTGTGTATAGCCAGCAGTGCAGAGAAATATTTAAACTAGAAC (SEQ ID NO 29) TTCTTCATTTATAACATGAGGGGCTTGGCTAGATATTTAACAGCCTGC (SEQ ID NO 30) GCTAGATATTTAACAGCCTGCTGTATTGACACCTTAGCATCAGGAAAT (SEQ ID NO 31) ATTTGAGTTATGTATATGAGAGACTGGGTACATCCTTTTACTTGTTTT (SEQ ID NO 32)
TMD0888 (SEQ ID NO 33-34)	GGAAGTGGAGCCAGGTA GCAGAAATTCATC (SEQ ID NO 35)	GGAGCAGAGGATCAGGAGG AAGGTG (SEQ ID NO 36)	ACACTGCAGTTATATAGGGTGGCCAGGTAGTTGAGCTGGTGAATTTGA (SEQ ID NO 37) GCAGTGTGACATTTAAAGAGTGGGGCATGGAGGAGAACTAAAGTTGGAG (SEQ ID NO 38) ATTCAGATTTATATATTTGGTCCAGTACGGTATCAATATATTATCAGTA (SEQ ID NO 39)
TMD0890 (SEQ ID NO 40-41)	TCACCACTCTGGGACG GTACAACCT (SEQ ID NO 42)	GGCCACACCAATCAGTGTG CAT (SEQ ID NO 43)	CAATCTGTATTTATACGGCTCTACATCCAGTACCTGCTTATGTA (SEQ ID NO 44) GTTCTCTTTTATAAAGGCTATGTGGGACTTGGCAAACTCTAGTGGCC (SEQ ID NO 45) CAACATGAAATATAAGTAGGGGAGTATCTTGGGTAGAAAGGATGCCGAG (SEQ ID NO 46)
TMD1780 (SEQ ID NO 47-48)	CTCTGAATCTTCTACAC AACTGTTATCTGCCCA (SEQ ID NO 49)	ATGAGATGGGAGCAGAGGT GGAGAAG (SEQ ID NO 50)	ATCAATATGTTAAATGGCCGTACTGTCAAAAGCAATTTACAGATTCAA (SEQ ID NO 51) ATATGAAACCAAAAGCCCTCAAAATAGCCCAAGTAACCCCTAAAGAAAAA (SEQ ID NO 52) CGCCCTATCAATAAATGGTGTGGGAATAGCTGGGTAGCCAATCTGCAGAA (SEQ ID NO 53) CATAAGGTTCTTAAATTTGGGAGAGAGAAATCAGAAAGTCAGAGAAAGAG (SEQ ID NO 54)
TMD1781 (SEQ ID NO 55-56)	ATGACAGTTTATGATTC TATGTTGCCATCTGC (SEQ ID NO 57)	TCAGGATGGTGTGMAAATG AAGCCATAG (SEQ ID NO 58)	TTCCCTATTTAATAATGGTGTGGGAAAACTGGCTAGCCATATGTAGAA (SEQ ID NO 59) AACAACCCATCAAAAGTGGGCCAAAGATATGAACAGACACTTCTCAA (SEQ ID NO 60) AATGGCGATCAATTTAAAGTACGAAACAAACAGGTGCTGGAGAGGATGTG (SEQ ID NO 61) CCAGAGGATTTAAATCATCTGCTGTAAAGACACATGCCCACTGTATGT (SEQ ID NO 62)

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TABLE 6

SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
63,64	TMD0785	XM 060310	kidney	65-68	69,70

	XM_062147	XM_061676
outside	1-27	1-28
TM (1)	28-50	29-51
inside	51-61	52-62
TM (2)	62-84	63-85
outside	85-98	86-99
TM (3)	99-121	100-122
inside	122-140	123-133
TM (4)	141-163	134-156
outside	164-203	157-201
TM (5)	204-226	202-224
inside	227-237	225-236
TM (6)	238-260	237-259
outside	261-274	260-273
TM (7)	275-293	274-296
inside	294-313	297-314

TABLE 7

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Clone ID (gene code)	Accession	Gene Name/Description	Predominant sites of expression	Other expression sites
TMD0049	XM_057351	Homo sapiens similar to organic anion transporter 4 like protein (LOC118085) mRNA	kidney	none
TMD0190	XM_087157	Homo sapiens similar to sodium-coupled ascorbic acid transporter 2 (LOC151295) mRNA	kidney	colon and liver
TMD0242	XM_088369	Homo sapiens similar to unnamed protein product (LOC157724) mRNA	kidney	none
TMD0335	XM_089960	Homo sapiens similar to sodium iodide symporter (LOC159963) mRNA	kidney	adrenal gland, heart, intestine (small), liver, muscle, testis
TMD0371 (new)	XM_089732	Homo sapiens similar to CG8271 gene product (LOC196023) mRNA	kidney	pancreas and testis
TMD0374 (new)	XM_085595	Homo sapiens similar to unnamed protein product (LOC146802) mRNA	kidney	brain, muscle, ovary, skin, testis
TMD0469	XM_038736	Homo sapiens solute carrier family 4 sodium bicarbonate cotransporter member 9 (SLC4A9) mRNA	kidney	none
TMD0719	XM_059548	Homo sapiens hypothetical gene supported by XM_059548 (LOC131920) mRNA	kidney	none
TMD0731	XM_059703	Homo sapiens similar to putative (H. sapiens) (LOC134288) mRNA	kidney	adrenal gland, muscle, thyroid
TMD0785	XM_060310	Homo sapiens similar to olfactory receptor MOR275-2 (LOC127069) mRNA	kidney	none
TMD0841	XM_060623	Homo sapiens similar to KIAA0711 gene product (H. sapiens) (LOC127707) mRNA	kidney	lung
TMD1114	NM_019841	Homo sapiens transient receptor potential cation channel subfamily V member 5 (TRPV5) mRNA	kidney	none
TMD1148	XM_087108	Homo sapiens similar to calcium channel voltage-dependent gamma subunit 6 (LOC151151) mRNA	kidney	none

TABLE 8

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TABLE 9

Gene Code	SEQ ID NO	Protein seq length(aa)	domain description
TMD0049	2	332	Sugar (and other) transporter: 2 - 302 Transmembrane domain: 12 - 34 Transmembrane domain: 39 - 58 Transmembrane domain: 131 - 153 Transmembrane domain: 157 - 179 Transmembrane domain: 186 - 205 Transmembrane domain: 215 - 237
TMD0190	4	243	Permease family: 91 - 224
TMD0242	6	470	AA-permease: 27 - 356 Transmembrane domain: 13 - 35 Transmembrane domain: 50 - 72 Transmembrane domain: 93 - 115 Transmembrane domain: 137 - 154 Transmembrane domain: 161 - 183 Transmembrane domain: 207 - 229 Transmembrane domain: 242 - 264 Transmembrane domain: 286 - 308 Transmembrane domain: 335 - 357 Transmembrane domain: 362 - 379 Transmembrane domain: 392 - 414 Transmembrane domain: 420 - 442

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TMD0335	8	178	Sodium solute symporter family: 41 - 172
TMD0371	10	516	Transmembrane domain: 45 - 67
			Transmembrane domain: 87 - 109
			Transmembrane domain: 116 - 138
			Transmembrane domain: 143 - 165
			Transmembrane domain: 174 - 196
			Transmembrane domain: 201 - 223
			Transmembrane domain: 283 - 305
			Transmembrane domain: 320 - 339
			Transmembrane domain: 351 - 370
			Transmembrane domain: 375 - 397
			Transmembrane domain: 404 - 426
			Transmembrane domain: 441 - 463
TMD0374	12	566	Transmembrane domain: 31 - 53
			Transmembrane domain: 68 - 90
			Transmembrane domain: 116 - 138
			Transmembrane domain: 153 - 171
			Transmembrane domain: 184 - 206
			Transmembrane domain: 211 - 233
			Transmembrane domain: 254 - 273
			Transmembrane domain: 288 - 310
			Transmembrane domain: 331 - 353
			Transmembrane domain: 373 - 395
			Transmembrane domain: 404 - 426
			Transmembrane domain: 431 - 453
			Transmembrane domain: 542 - 564

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TMD0469	14	983	HCO3- transporter family: 108 - 891
			Transmembrane domain: 413 - 435
			Transmembrane domain: 447 - 469
			Transmembrane domain: 498 - 520
			Transmembrane domain: 532 - 554
			Transmembrane domain: 623 - 645
			Transmembrane domain: 665 - 684
			Transmembrane domain: 712 - 731
			Transmembrane domain: 751 - 773
			Transmembrane domain: 813 - 832
			Transmembrane domain: 839 - 858
			Transmembrane domain: 897 - 919
TMD0719	16	146	Transmembrane domain: 7 - 29
			Transmembrane domain: 49 - 71
TMD0731	18	218	Transmembrane domain: 38 - 60
			Transmembrane domain: 70 - 92
TMD0785	20	312	7 transmembrane receptor (rhodopsin family): 58 - 290
			Transmembrane domain: 29 - 51
			Transmembrane domain: 61 - 83
			Transmembrane domain: 140 - 162
			Transmembrane domain: 197 - 219
			Transmembrane domain: 240 - 262
			Transmembrane domain: 272 - 294
TMD0841	22	1161	Kelch motif: 850 - 895
			Kelch motif: 897 - 938

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TMD1114	24	729		Transmembrane domain: 327 - 349
				Transmembrane domain: 383 - 405
				Transmembrane domain: 420 - 438
				Transmembrane domain: 451 - 473
				Transmembrane domain: 493 - 512
				Transmembrane domain: 519 - 541
				Transmembrane domain: 554 - 576
TMD1148	26	103		Transmembrane domain: 7 - 24
				Transmembrane domain: 39 - 61
				Transmembrane domain: 68 - 90

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Gene ID (gene code)	ACCN	Cytogenetic locus	Disease/Linkage
TMD0049	XM_057351	11q12.1	osteoporosis-pseudoglioma syndrome; spastic paraplegia 1 7
TMD0190	XM_087157	2q36.2	none
TMD0242	XM_088369	8q21.2	none
TMD0335	XM_089960	11p14.2	none
TMD0371A	XM_089732	10q23.33	epilepsy, partial, with auditory features; spastic paraplegia 9, autosomal dominant
TMD0374	XM_085595	17p11.2	smith-magenis syndrome
TMD0469	XM_038736	5q31	paget disease of bone 4
TMD0719	XM_059548	3q29	none
TMD0731	XM_059703	5q13.2	spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuropathy
TMD0785	XM_060310	1q44-tel	familial cold urticaria (FCU); Muckle-Wells syndrome (MWS); susceptibility
TMD0841	XM_060623	1p36.13	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility; melanoma, cutaneous
TMD1114	NM_019841	7q35	glaucoma 1, open angle, f
TMD1148	XM_087108	2q14.1	motor neuropathy, distal hereditary, with vocal cord paralysis; cardiomyopathy, dilated, 1h

TABLE 10



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CODE (SEQ ID NO)	DIAGNOS (SEQ ID NO)	PROMOTERS (SEQ ID NO)
TMD0049 (78,79)	CGGTTCCGACCTGTATCTCCAC (104) CAAGCTCTGGTCTCGGCGAAG (105)	AAAGAGCCTCTAAAGAAGGGTTCCAGACTACAGGAGCTCACTGGAATA (106)
TMD0190 (80,81)	ACCATCTGCAAACTTGGATGGC (107)	GCTTATGTATGAAAAACCTGTTTATCTGAGCCTAGAACTGCTTTTC (109)
TMD0242 (82,83)	AAGGAGCCGGAACAGACAGGAGG (108) GAGTCTCCTGTGCGTTTGGCTG (111)	AGTGATAGTTTTAAATGGGAGGAATAAGTCTGCAAAATTTCCCATAT (110)
TMD0335 (84,85)	AAGTGTAAAGCATGCCCGCCTGA (112)	AGTCCAGCTTAAAGAAGACACACAGACAGAGAGAGAGACAGAG (113)
TMD0371 (86,87)	GTTCCGCTATGCTGCCACGGTCATC (115) AGTCTGCGAGTCTCGCATTTGTG (116)	TTAGTGAATTTAAAAAATGTGAAGAAGAGAGAGTCAAGGCAATRAAGGA (114)
TMD0374 (88,89)	CAGGATTAGGCACAAACGGCATGG (119)	GATACAAATAATTAAGAAGCCAGGTTAAGGTAAATATTTAAAGACCAAG (117)
TMD0469 (90,91)	TGGAGGCGAGATAGCAGAGCCC (120) CTGCTCTGGGACCCCTGATAAGC (122)	ATCTCAGCAATTAATAAATGCTGAGTGGTAAATTTGTTATCAATTTCTATGT (118)
TMD0719 (92,93)	CCGAGGCTGTGGTTCAGTGTCTC (123) CTGAGGTGTCCCTCCCAAGCAGGT (126)	CTAGACTATTTAAAAAACCCTTGCTTGCCAGAGTGGCTCAAGCCTGTAA (121)
TMD0731 (94,95)	TACGCGCGAGAGCACTGGAGATG (127) GTCACCTCAGCGATCTCAACGATAGG (131)	AGCTGCTCCTATTAAAAAGTGACCTGGAGTGAGATGGATTCTTCTGCCTAT (124)
TMD0785 (96,97)	TGAGCAGGAACAGGATATAGGTACGG (132) GGGTGGGAAGGAAGCAGGGAAGAG (135)	CCAAATTTCTGAAAAACGGGAGTCACGTGGGCACCATCACGCCCGGGT (125)
TMD0841 (98,99)	CCAGCTAGTTTCATGTTGGCGCAG (136) CTGTTGGAAATCTTCAGCCAGATCTCACAC (138) ATGAGAGTTCTGCAGCTCAGCA (139)	TAAACAAATACATAAATGAGCGAGTTACTAGTAGTGTTACTGCTAGGAA (128)
TMD1114 (100,101)	GGGCCACTTCCACAGACAGGAAGC (142) TGGCCTGAGAGGTAGATTCCACATAGTACTCGT (143)	ACTAAAAATATAAAATCAGCCAGGCTGGTGGCACATGCTGTGTAATCTC (129)
TMD1148 (102,103)	CTCCTTTCTGGTCAGAGAACAGACTGGAC (145) GTGATGTCTCGAGAAATGAGTGGGTTG (146)	GGGATGCATTATAAATGCAACCCAGCCAGAGGCCCCCTGGCTTCAGAACCT (130)
		ATATACCTTGTTTAAAGAGGGGTATTATCACAATAAAACAGGAAAGCT (133)
		ACCCCTACTTTTAAAGGCCCTTGACAAACAGTCTAAAGTTCTCACCTTAA (134)
		TTATTGGGCATAAAAATATGAAGAGAGGTCCACAGAGAGTCCCTAGGTTCT (137)
		AAGCAATTTGTTAAAAACTGGCATTACTTTACTTCTTATGCTTTCTGTGTC (140)
		ACTTTAAATTTTAAAGAAGGTTTACATCAAGAAATTTCCAAAGTGAGGTTT (141)
		AAGGCTTCTTCAAAAAAAGCGGGCTTGTCTGGGCCAGAAATCAGAGTG (144)
		CAGCGAGGCGAGAAAAATGTCCCAAGATTGAGCCCTCCCACTCCCAAGTG (147)
		TAATATRAAATATATAAATAGTGCACATTAATTTACTTCTCTGCTGTT (148)
		GCCAGAGAGTTTAAATGAAGCCCTACTTTTGGGCGAGAGCGGGAGGAAC (151)

TABLE 11

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SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	OTHER SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
152, 153	TMD0986	XM_061779	pancreas	low levels in testis	156-161	154,155
162, 163	TMD0987	XM_061780	pancreas	low levels in testis	166	164,165
167, 168	TMD0353	XM_061781	pancreas			169,170
171, 172	TMD0989	XM_061784	pancreas			173,174
175, 176	TMD058	XM_061785	pancreas	low levels in testis	179,180	177,178

TABLE 12

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	XM_061779	XM_061780	XM_061781	XM_061784	XM_061785
outside	1-23	1-25	1-22		1-24
TM (1)	24-46	26-48	23-45		25-47
inside	47-58	49-60	46-65		48-59
TM (2)	59-78	61-83	66-88		60-82
outside	79-97	84-97	89-97		83-96
TM (3)	98-120	98-120	98-120		97-119
inside	121-140	121-139	121-140		120-139
TM (4)	141-163	140-162	141-163		140-162
outside	164-198	163-202	164-203		163-201
TM (5)	199-221	203-25	204-226		202-224
inside	222-240	226-237	227-237		225-236
TM (6)	241-260	238-260	238-260		237-259
outside	261-274	261-269	261-272		260-268
TM (7)	75-292	270-289	273-292		269-291
inside	293-314	290-318	293-323		292-311

TABLE 13

GENBANK IDENTIFIER	MOUSE HOMOLOG	061779	061780	061781	061784	061785
XM_061779			42% (63%)	36% (57%)	43% (64%)	40% (61%)
XM_061780	MOR239-6 (AY073489) 90% (93%)	42% (63%)		41% (60%)	44% (62%)	46% (67%)
XM_061781		36% (57%)	41% (60%)		43% (63%)	40% (61%)

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XM_061784	MOR223 ~>85%	43% (64%)	44% (62%)	43% (63%)	81% (87%)
XM_061785	MOR223 ~>85%	40% (61%)	46% (67%)	40% (61%)	81% (87%)

TABLE 14

TABLE 15

Clone ID (gene code)	ACCN	Predicted Structure Expression	Other expression sites	Cytogenetic locus
TMD1030 (SEQ ID NO 185-186)	XM_166853	spleen	liver	11q12.2
TMD1029 (SEQ ID NO 187-188)	XM_166854	spleen, lymphocytes, liver	brain, heart, lung, lymph node	11q12.2
TMD1028 (SEQ ID NO 189-190)	XM_166855	spleen, lymphocytes	liver	11q12.2
TMD0621 (SEQ ID NO 191-192)	XM_166205	spleen	brain, heart, liver, lung and pancreas	11q12.2

TABLE 16

Clone ID	ACCN	Protein length (aa)	domain description
TMD1030	XM_166853	298	Transmembrane domain: 27 - 49 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 175 - 197 Transmembrane domain: 207 - 226

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TMD1029	XM_16684	309	Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292  Transmembrane domain: 26 - 48 Transmembrane domain: 61 - 78 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 196 - 218 Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292
TMD1028	XM_166855	173	Transmembrane domain: 18 - 40 Transmembrane domain: 61 - 83 Transmembrane domain: 103 - 125 Transmembrane domain: 137 - 156
TMD0621	XM_166205	109	Transmembrane domain: 9-31 Transmembrane domain: 69 - 91

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TABLE 17

Clone ID	ACCN	5'-UTR	3'-UTR
TMD1030	XM_166853	GGGATTTGGTGTCCACACGAATTCA (SEQ ID NO 197)	GAGCCTATATATATAGGCCAGCTACGAGTTGGA (SEQ ID NO 198)
TMD1029	XM_166854	GTCACCTGAATTCATCTCTCTGGGATTGGTGC (SEQ ID NO 199)	AAACCTGTTGTACAGAGGCCATTTATTGAGCC (SEQ ID NO 200)
TMD1028	XM_166855	GATATCATTTTGGGGCTGCATGATACAATTATGG (SEQ ID NO 201)	CTCCACCCAGTGAACATCAAGTTTAAATCCCAC (SEQ ID NO 202)
TMD0621	XM_166205	TTAAGCTATTAGTTAGTTTCATATGTCATGGGTTTCC (SEQ ID NO 203)	CTCATTAATACGATGGCATAGATACATGTAAGAGAG (SEQ ID NO 204)

TABLE 18

Clone ID	ACCN	Promoter Sequence (likelihood score)
TMD1030	XM_166853	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCACTACCCACTTGTAG (0.94) (SEQ ID NO 205) ACATCCATTATATAACAGGGTTAATATATCTTGTAAAGATAGCACCTAGA (0.95) (SEQ ID NO 206)
TMD1029	XM_166854	AAATGTATAAATTCCTGCATGAATTTGGGGTGGGCTTGTACTACTTTTG (0.98) (SEQ ID NO 207)
TMD1028	XM_166855	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCACTACCCACTTGTAG (0.94) (SEQ ID NO 208) ACATCCATTATATAACAGGGTTAATATATCTTGTAAAGATAGCACCTAGA (0.95) (SEQ ID NO 209)

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TMD0621	XM_166205	AAATATATATTTAAATTGGCCAGCGCGGTGGCTCAGCCTATATCCC (0.99) (SEQ ID NO 210) GGCTCAGCGCTATATCCAGCACCTTTGGAGGCGGAGCGGTGGATCA (0.97) (SEQ ID NO 211) TCCCAATATATATATATACACACACACACACACATATAT (1.00) (SEQ ID NO 212) CACACACATATATATACACACATATTTTATATCATTTAACAACA (0.91) (SEQ ID NO 213)
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TABLE 19

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**TABLE 19**

*(from Principles of Internal Medicine, Volume 1, Page 357, 12<sup>th</sup> Edition, McGraw-Hill Inc.)*



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Table 20

GeneID	AGCN	Gene Name/Description	Predominant sites of expression	Other expression sites
TMD0077	XM_166914	Homo sapiens olfactory receptor MOR212-1 (LOC219956), mRNA.	pancreas and testis	brain, heart and kidney
TMD0233	XM_069616	Homo sapiens similar to olfactory receptor (LOC135941) mRNA	pancreas	none
TMD0256	XM_066725	Homo sapiens similar to olfactory receptor (LOC139478) mRNA	pancreas	skin and testis
TMD0258	XM_066873	Homo sapiens similar to beta-2 adrenergic receptor (LOC139760) mRNA	pancreas	colon, stomach and testis
TMD0267	XM_089550	Homo sapiens similar to CG5281 gene product (LOC159371) mRNA	pancreas and testis	adrenal gland, bone marrow, colon, heart, intestine (small), kidney, liver, pituitary, prostate, skin, stomach and thyroid
TMD0271	XM_061815	Homo sapiens similar to odorant receptor S18 gene (LOC120010) mRNA	pancreas and testis	PBL, prostate, thymus and uterus
TMD0290	XM_065813	Homo sapiens similar to unnamed protein product (LOC130644) mRNA	pancreas and testis	none
TMD0530	XM_048304	Homo sapiens hypothetical protein DKFZp564A1164 (DKFZP564A1164) mRNA	pancreas	brain, kidney, lung, lymph node, PBL, mammary gland, pituitary, stomach, testis and thyroid
TMD0574	XM_055514	Homo sapiens KIAA1910 protein (KIAA1910) mRNA	brain and pancreas	pituitary
TMD0608	XM_058332	Homo sapiens similar to putative (H. sapiens) (LOC118670) mRNA	pancreas and testis	stomach
TMD0639	XM_058690	Homo sapiens similar to data source/MD, source key:MG196073, evidence:ISS-hexosaminidase A-putative (LOC204249), mRNA.	pancreas and testis	liver, PBL and prostate
TMD0645	XM_085376	Homo sapiens LOC146225 (LOC146225), mRNA.	pancreas and testis	bone marrow, brain, heart, kidney, liver, lung, lymph node, PBL, muscle, pituitary, prostate, skin, spleen, stomach and thymus
TMD0674	XM_059132	Homo sapiens similar to RIKEN cDNA 4930549C01 gene (LOC127309) mRNA	pancreas and testis	brain, pituitary, prostate and stomach
TMD0675	XM_059134	Homo sapiens similar to putative (H. sapiens) (LOC127348) mRNA	pancreas and testis	prostate and stomach
TMD0677	XM_059140	Homo sapiens similar to dJ39622.2 (novel protein) (H. sapiens) (LOC127391) mRNA	pancreas and testis	prostate and stomach
TMD0726	XM_059639	Homo sapiens similar to hypothetical protein (H. sapiens) (LOC133309) mRNA	pancreas and testis	adrenal gland, brain, prostate and stomach
TMD0727	XM_059654	Homo sapiens similar to testis-specific transporter TST1 (H. sapiens) (LOC133482) mRNA	pancreas and testis	stomach
TMD0739	XM_059812	Homo sapiens similar to putative (H. sapiens) (LOC135886) mRNA	pancreas and testis	liver, lung, mammary gland, ovary, pituitary, prostate and stomach
TMD0753	XM_059954	Homo sapiens similar to putative (H. sapiens) (LOC138240) mRNA	pancreas and testis	stomach
TMD1111	NM_014366	Homo sapiens polycystic kidney disease 2-like 2 (PKD2L2) mRNA	pancreas and testis	none
TMD1127	NM_054020	Homo sapiens putative ion channel protein CATSPER2 (CATSPER2), mRNA.	pancreas and testis	none

Table 21

Clone ID	ACCN	Protein seq length (aa)	Domain description
TMD0077	XM_166914	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domains: 27 - 49
			Transmembrane domains: 61 - 83
			Transmembrane domains: 98 - 120
			Transmembrane domains: 141 - 163
			Transmembrane domains: 202 - 224
			Transmembrane domains: 237 - 259
			Transmembrane domains: 274 - 291
TMD0233	XM_069616	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 26 - 48
			Transmembrane domain: 60 - 77
			Transmembrane domain: 97 - 119
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 261
			Transmembrane domain: 272 - 291
TMD0256	XM_066725	308	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 27 - 49
			Transmembrane domain: 61 - 83
			Transmembrane domain: 98 - 120
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 258
			Transmembrane domain: 273 - 291
TMD0258	XM_066873	335	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 10 - 32
			Transmembrane domain: 39 - 61
			Transmembrane domain: 79 - 101
			Transmembrane domain: 121 - 143
			Transmembrane domain: 163 - 185
			Transmembrane domain: 226 - 248
			Transmembrane domain: 263 - 282
TMD0267	XM_089550	324	Integral membrane protein DUF6: 49-161
			Transmembrane domain: 59 - 78
			Transmembrane domain: 91 - 110
			Transmembrane domain: 115 - 137
			Transmembrane domain: 146 - 168
			Transmembrane domain: 183 - 201
			Transmembrane domain: 214 - 236
			Transmembrane domain: 246 - 265

			Transmembrane domain: 270 - 292
			Transmembrane domain: 297 - 316
TMD0271	XM_061815	291	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 29 - 51
			Transmembrane domain: 56 - 78
			Transmembrane domain: 83 - 105
			Transmembrane domain: 120 - 142
			Transmembrane domain: 163 - 185
			Transmembrane domain: 190 - 207
			Transmembrane domain: 220 - 239
			Transmembrane domain: 249 - 271
TMD0290	XM_065813	245	Transmembrane domain: 24 - 46
			Transmembrane domain: 61 - 83
			Transmembrane domain: 96 - 118
			Transmembrane domain: 128 - 150
			Transmembrane domain: 162 - 184
			Transmembrane domain: 221 - 243
TMD0530	XM_048304	708	Immunoglobulin domain: 139-206
			Immunoglobulin domain: 326-377
			Transmembrane domain: 511 - 533
TMD0574	XM_055514	696	Leucine rich repeat C-terminal domain: 212-262
			Leucine rich repeat C-terminal domain: 529-579
			Transmembrane domain: 621 - 643
TMD0608	XM_058332	105	Transmembrane domain: 13 - 35
TMD0639	XM_058690	127	Transmembrane domain: 12 - 34
			Transmembrane domain: 44 - 66
TMD0645	XM_085376	248	Transmembrane domain: 113 - 135
			Transmembrane domain: 150 - 169
			Transmembrane domain: 176 - 198
TMD0674	XM_059132	134	Transmembrane domain: 5 - 22
TMD0675	XM_059134	206	Transmembrane domain: 15 - 37
TMD0677	XM_059140	182	Transmembrane: 49 - 71
TMD0726	XM_059639	96	Transmembrane domain: 13 - 35
			Transmembrane domain: 50 - 72
TMD0727	related to XM_059654	719	Transmembrane domain: 108 - 130

			Transmembrane domain: 145 - 164
			Transmembrane domain: 171 - 193
			Transmembrane domain: 229 - 251
			Transmembrane domain: 264 - 286
			Transmembrane domain: 314 - 336
			Transmembrane domain: 421 - 443
			Transmembrane domain: 453 - 475
			Transmembrane domain: 580 - 602
			Transmembrane domain: 668 - 690
			Organic Anion Transporter Polypeptide (OATP) family, C-terminus: 125-473
			Organic Anion Transporter Polypeptide (OATP) family, N-terminus: 558-717
TMD0739	XM_059812	265	Transmembrane domain: 126 - 148
			Transmembrane domain: 185 - 207
TMD0753	XM_059954	161	Transmembrane domain: 26 - 48
TMD1111	NM_014386	609	Ion transporter domain: 284-490
			Transmembrane domain: 34 - 56
			Transmembrane domain: 274 - 296
			Transmembrane domain: 315 - 337
			Transmembrane domain: 364 - 386
			Transmembrane domain: 407 - 429
			Transmembrane domain: 469 - 491
TMD1127	NM_054020	528	Ion transporter domain: 172-340
			Transmembrane domain: 113 - 132
			Transmembrane domain: 147 - 169
			Transmembrane domain: 176 - 198
			Transmembrane domain: 241 - 263
			Transmembrane domain: 276 - 295
			Transmembrane domain: 315 - 337

Table 22

Gene ID	ACCN	Cytogenetic locus	Disease linkage
TMD0077	XM_166914	11q12.2	angioedema, hereditary; spastic paraplegia 17; osteoporosis-pseudoglioma syndrome; pancreatic tumor
TMD0233	XM_069616	7q35	glaucoma 1, open angle, f;
TMD0256	XM_066725	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0258	XM_066873	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0267	XM_089550	10q24.1	corneal dystrophy of bowman layer, type ii; alzheimer disease 6
TMD0271	XM_061815	11p15.4	charcot-marie-tooth disease, type 4b, form 2; deafness, neurosensory, autosomal recessive 18;
TMD0290	XM_065813	2p23.1	none
TMD0530	XM_048304	19q13.13	hypocalciuric hypercalcemia, familial, type iii; deafness, autosomal dominant nonsyndromic sensorineural 4; microcephaly, primary autosomal recessive, 2
TMD0574	XM_055514	13q31.1	microcoria, congenital; schizophrenia 7;
TMD0608	XM_058332	10q26.3	endometrial carcinoma
TMD0639	XM_058690	15q22.32	cataract, central sacular, with sutural opacities; obesity syndrome
TMD0645	XM_085376	16q23.1	dehydrated hereditary stomatocytosis; pancreatic acinar cancer
TMD0674	XM_059132	1p36.11	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility, melanoma, cutaneous malignant; inflammatory bowel disease 7;
TMD0675	XM_059134	1p33	carcinoma of pancreas
TMD0677	XM_059140	1p34.2	deafness, autosomal dominant nonsyndromic sensorineural 2; porphyria cutanea tarda; hypercholesterolemia, familial, ptosis, hereditary congenital 1;
TMD0726	XM_059639	10q11.22	none
TMD0727	related to XM_059654	5q21.1	anemia, dyserythropoietic congenital, type iii; dyslexia, specific, 1; colorectal cancer, hereditary nonpolyposis, type 7; cataract, central sacular, with sutural opacities
TMD0739	XM_059812	7q11.23	autism, susceptibility to, 1; muscular dystrophy, limb-girdle, type 1d; aneurysm, intracranial
TMD0753	XM_059954	9q21.12	hemophagocytic lymphohistiocytosis, familial, 1; amyotrophic lateral sclerosis with frontotemporal dementia
TMD1111	NM_014386	5q31	none
TMD1127	NM_054020	15q13-q15	nanophthalmos 2; spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuronopathy; pancreatic acinar carcinoma

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TABLE 23

CODE	ACCN	PRIMERS	PROMOTER
TMID0077 (SEQ ID NO 214-215)	XM_166914	TCATGGATCACCAGCTCCACGCTC (Forward) (SEQ ID NO 256) CACCAAGATCACCAACCATGGAAAGCA (Reverse) (SEQ ID NO 257)	GGATTACGGCCTTTTAAACCCCACTCAGTGGTGCCATGGCAGGGCTTTGA (0.88) (SEQ ID NO 258)
TMID0233 (SEQ ID NO 216-217)	XM_069616	TGCTGACGAATCTTATGAACCAAG (Forward) (SEQ ID NO 259) TCACGTCAGCCTCTCTCTCTCAGTG (Reverse) (SEQ ID NO 260)	TCACAAATCATATAAAATTAGGGGAAAAGAGAGGAGGAGGATAGTACTATAAA (0.96) (SEQ ID NO 261) AATTCTTATTTTAAAGAGCCTCAGAAATGTCACCATGCTTAGTTATTTTA (0.95) (SEQ ID NO 262)
TMID0256 (SEQ ID NO 218-219)	XM_066725	GGCCATGGACAAATGTCACAGCAG (Forward) (SEQ ID NO 263) AGCAGACACATACTGGGCCATTTCATAACCAC (Reverse) (SEQ ID NO 264)	GGTACTATTCTATATTTTGGGCACACAGCAATGAAGAAAACAGAAAAACC (0.93) (SEQ ID NO 265) CTGGGTTTCATAAAATATGGAGCAGAAAGTTTTCACAAATATAGAACAGCA (0.92) (SEQ ID NO 266) TAGAAATGTGTTTATAAAAAATGAAGCAGGGCTAGGGGAAAGAGATGGGTGA (0.91) (SEQ ID NO 267)
TMID0258 (SEQ ID NO 220-221)	XM_066873	CCTCATTTGGCTTCTCCCACTCG (Forward) (SEQ ID NO 268) GCCATCAAACTCTGAGCTGGAGATAGTGAC (Reverse) (SEQ ID NO 269)	CCAGGAACTTTTAAAACTCCCAATGCAAGTTTACCACCCAGAAATATTA (0.97) (SEQ ID NO 270) CATCCTGGAATATATTTGGGTCCAACTCTGCACTTGTCTCTCTATTCCT (0.96) (SEQ ID NO 271) CTGGGGCCCTCAAAAAGCTCACCTTCCCTCACTTCCCACTTCAACTGAT (0.91) (SEQ ID NO 272)
TMID0267 (SEQ ID NO 222-223)	XM_089550	TGGCCTCGTTGAAAGTGTCATCATCC (Forward) (SEQ ID NO 273) TTGGTACCAATTTACGAAATGGCCGC (Reverse) (SEQ ID NO 274)	AAACGGCATTTTAAAAATGCAAGTTTAAATTTGTTATCCTCATCTATGGTT (0.98) (SEQ ID NO 275)
TMID0271 (SEQ ID NO 224-225)	XM_061815	CTGGACTTTGAGCAGTACCACGTCTGGATC (Forward) (SEQ ID NO 276) CATATTTCCACACCAATTTTGACAAATGG (Reverse) (SEQ ID NO 277)	ATTTGGTTATATAGAGGAGTCTAGGAAAAGACTCGTGGGTCTGATTC (0.97) (SEQ ID NO 278) TACTCATATTTATATAGCAGCAACTTACATTGACCCAGGGAGAACTCAGT (0.94) (SEQ ID NO 279)
TMID0290 (SEQ ID NO 226-227)	XM_065813	GTTACCCACCCAAACCGTCACGACC (Forward) (SEQ ID NO 280) CAGCGATGCCAGAGAAAGCAGATG (Reverse) (SEQ ID NO 281)	CTAGAAATTTACATAAAAAGGAGCTGGAGGAGCTTTTGCAGCAACTTTGCAT (0.97) (SEQ ID NO 282) TTTCTCTCTTTTAAAAACACGCTTTTCACTCTCAAAACAGCAGAGAAATGAA (0.98) (SEQ ID NO 283) AACTGGGTCTATAAGAGAGCCAGGGCACTTATTATCCAAAGGCGAGATG (0.99) (SEQ ID NO 284)
TMID0530 (SEQ ID NO 228-229)	XM_048304	CTATGACTTCAACCCACACTGGGCA (Forward) (SEQ ID NO 285) AAGGTGCGCAACTTGTCTCTGGCTC (Reverse) (SEQ ID NO 286)	GGCGGGAGTAAAAAGGAGAGGTCCAAATCCACGGGCCCCAGTGTGGGTG (0.86) (SEQ ID NO 287)



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CODE	ACCN	PRIMERS	PROMOTER
TMD0574 (SEQ ID NO 230-231)	XM_055314	TCAATGCCATGCCCAAACTGAGGA (Forward) (SEQ ID NO 288) CAACACCGAGATGGACACCCCTGCT (Reverse) (SEQ ID NO 289)	CTTTAAAGGTTTAAAAATGTGGGTTTATAGATGTTGTCCTTTCTAAACAGC (0.99) (SEQ ID NO 290) TCAGGATGCTCTAAAAAAGATCTCTCTAGTGTACACACGTCACACACACA (0.97) (SEQ ID NO 291) AGTAACTCTATTAAAAAGACCTAAAAATTTCAAAATCCTAAAAATGATCTAT (0.90) (SEQ ID NO 292) AATAAATGTTTTAAAAAGCACCTCTTTCCGAATGGTGGAGCTGGTGGGGC (0.91) (SEQ ID NO 293)
TMD0608 (SEQ ID NO 232-233)	XM_058332	CTCAGGACGAAAGATCATGATCGGCATC (Forward) (SEQ ID NO 294) GAAGATTTTGTGCCAGCTTTCCCAAG (Reverse) (SEQ ID NO 295)	TATCTCACTTATAAGTGGGAGCTAAGCCATGAGGGCACCAAGGCATAAG (0.99) (SEQ ID NO 296) TTACATATGTATACATGTGCCATGTGTGCTGCTGCCACCCATTAACTCGT (0.96) (SEQ ID NO 297)
TMD0639 (SEQ ID NO 234-235)	XM_058690	TCCATGCTCAGCTTCATCTCAGCTACC (Forward) (SEQ ID NO 298) TCCATCTCAGACCTTTGGCCCTTCA (Reverse) (SEQ ID NO 299)	AAATAACCCCAATAAAAAAGTGGGCAAGGGCATGAACACTTTTCAAAAGA (1.00) (SEQ ID NO 300)
TMD0645 (SEQ ID NO 236-237)	XM_085376	AGGACGGTAAGGAGCCATCGGACA (Forward) (SEQ ID NO 301) CTTGCCAGGTTCTGGTGGCTTGG (Reverse) (SEQ ID NO 302)	TCTTTTGTCTATAAATAGGACTTTTGAATTTTCTGGACTAGAGAAATTGTAT (0.94) (SEQ ID NO 303)
TMD0674 (SEQ ID NO 238-239)	XM_059132	ACGACTCCAAGAACAGCAAGGCCG (Forward) (SEQ ID NO 304) AAGGTAACATCGGCAGAGGCCAGC (Reverse) (SEQ ID NO 305)	GCTAGCATTTTTAAAAAGCTGATGTCTTCTCACTGGGCACGGGACTCACAC (0.94) (SEQ ID NO 306)
TMD0675 (SEQ ID NO 240-241)	XM_059134	CGGCCAGGTACCAAAAGCTCAGCTG (Forward) (SEQ ID NO 307) GCCAGATTCAGGAGGGGAATGGAAAGAGAAC (Reverse) (SEQ ID NO 308)	TGATCTACTTTTTAAAAAGGATCATGCTGGCTGCTGGTGGGATTAGGATA (0.91) (SEQ ID NO 309) TGATAGTGATAAAAAAAGTGGCCAGATTTTGGTTATATTTTGAATAAA (0.99) (SEQ ID NO 310) TATAGTGATAATTTAAAGCCAGGGTCTGGTGAGATAACTGATGGAATGA (0.93) (SEQ ID NO 311) ATTGGAGGACTATAAAGAGGGGAGTCATTAATAATGGTGTAAAGAGCTGA (0.96) (SEQ ID NO 312) AGAGGGAGTCAATTAATAATGGTGTAAAGAGCTGAGCTACAGCAGTGGT (0.97) (SEQ ID NO 313) GACATTCCACCCCAAAAAATGCCACTGGATGAAGTCCCTCTCTCCATTAA (0.92) (SEQ ID NO 314)



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**CLAIMS:**

1. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), or TMD0890 (XM\_060959) of claim 28, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

2. A method of claim 1, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

3. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), or TMD0890 (XM\_060959) of claim 28, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

4. A method of claim 3, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

5. A method of delivering an agent to an immune cell, comprising:

contacting an immune cell with an agent coupled to binding partner specific for a polypeptide coded for by TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), or TMD0890 (XM\_060959) of claim 28, whereby said agent is delivered to said cell.

6. A method of claim 5, wherein the agent is a therapeutic agent or an imaging agent.

7. A method of claim 5, wherein the agent is cytotoxic.

8. A method of claim 5, wherein the binding partner is an antibody.

5

9. A method of modulating the maturation of an immune system cell, comprising:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28, whereby the maturation of an immune cell is modulated.

10

10. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

15

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28, whereby the interaction is modulated.

20

11. A method of expressing a heterologous polynucleotide in immune system cells, comprising:

expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS 5, 10, 11, 16-19, 29-32, 37-39, 44-46, 51-54, and 59-62.

25

12. A method of treating an immune system disease, comprising:

administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025

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(XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28.

13. A method of claim 12, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

14. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28 in a tissue sample comprising immune system cells.

15. A method of claim 14, wherein assessing is: measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

16. A method of claim 14, wherein said assessing detecting is performed by: Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and using a polynucleotide probe having a sequence selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28, or a polynucleotide probe having 95% sequence identity or more to a sequence set forth in SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55, effective specific fragments thereof, or complements thereto.

17. A method of assessing a therapeutic or preventative intervention in a subject having an

immune system disease, comprising,

determining the expression levels of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28 in a tissue sample comprising immune system cells.

18. A method of claim 17, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

19. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of a gene selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) of claim 28, or the biological activity of a polypeptide encoded thereby, in said immune system cell, and

determining whether said test agent modulates said gene or polypeptide.

20. A method of claim 19, wherein said agent is an antisense polynucleotide which is effective to inhibit translation of said gene or an antibody specific for said polypeptide.

21. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising: comparing the structure of:

genomic DNA or RNA or cDNA or a polypeptide comprising all or part of a gene selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890

(XM\_060959) of claim 28 with the structure of SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55.

22. A method of claim 20, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

5 23. A method of identifying a genetic basis for an immune disease or disease-susceptibility, comprising:

determining the association of an immune disease or disease-susceptibility with a nucleotide sequence present in a genome comprising the gene complex of claim 28.

10 24. A method of claim 23, wherein determining is performed by producing a human-linkage map of said complex.

25. A method of claim 23, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having an immune system disease.

15

26. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a functional disruption of a gene selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888

20 (XM\_060957), and TMD0890 (XM\_060959) of claim 28, or a mouse homolog thereof, and which has a defect in immune system function.

27. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:



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displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for a gene selected from TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890

5 (XM\_060959), or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

28. A composition consisting essentially of the Iq22 immune gene complex, comprising

10 TMD0024 (XM\_060945), TMD1779 (XM\_060946), TMD0884 (XM\_060947), TMD0025 (XM\_060948), TMD1780 (XM\_089422), TMD1781 (XM\_089421), TMD0304 (XM\_060956), TMD0888 (XM\_060957), and TMD0890 (XM\_060959) genes, or a fragment thereof comprising at least two said genes.

15 29. A composition of claim 28, wherein said complex consists essentially of the chromosome region between STS markers SHGC-81033 and SHGC-145403, or a fragment thereof comprising at least two said genes.

30. A composition of claim 28, wherein said complex consists essentially of the  
20 chromosome region between STS markers SHGC-81033 and DIS3249, G15944, GDB:191077, or GDB:196442, or a fragment thereof comprising at least two said genes.

31. A composition of claim 28, wherein said complex consists essentially of the  
25 chromosome region between STS markers RH118729 and DIS2577 or SHGC-145403, or a fragment thereof comprising at least two said genes.

32. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for a XM\_062147 (SEQ ID NO 63) or XM\_061676 (SEQ ID NO 69) of claim 59 under conditions effective for  
30 said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

33. A method of claim 32, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

5 34. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for XM\_062147 (SEQ ID NO 64) or XM\_061676 (SEQ ID NO 70) of claim 59 under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

10

35. A method of claim 34, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

36. A method of delivering an agent to an immune cell, comprising:

15

contacting an immune cell with an agent coupled to binding partner specific for XM\_062147 (SEQ ID NO 64) or XM\_061676 (SEQ ID NO 70) of claim 59, whereby said agent is delivered to said cell.

37. A method of claim 36, wherein the agent is a therapeutic agent or an imaging agent.

20

38. A method of claim 36, wherein the agent is cytotoxic.

39. A method of claim 36, wherein the binding partner is an antibody.

25 40. A method of modulating the maturation of an immune system cell, comprising:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the maturation of an immune cell is modulated.

30 41. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the interaction is modulated.

- 5     42. A method of expressing a heterologous polynucleotide in immune system cells, comprising:
- expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 65, 66, 72, 73, 74, or 75.

10

43. A method of treating an immune system disease, comprising:
- administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59.

15

44. A method of claim 43, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

20

45. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:
- assessing the expression of a gene, or polypeptide encoded thereby, selected from XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

25

46. A method of claim 45, wherein assessing is:
- measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

30

47. A method of claim 45, wherein said assessing detecting is performed by:
- Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

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RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 67, 68, 76, and 77.

- 5 48. A method of assessing a therapeutic or preventative intervention in a subject having an immune system disease, comprising,
- determining the expression levels of a gene, or polypeptide encoded thereby, selected from XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

10

49. A method of claim 48, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

50. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

15

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59, or a polypeptide encoded thereby, in said immune system cell, and

20

determining whether said test agent modulates said gene.

51. A method of claim 50, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NOS 63 or 69 and which is effective to inhibit translation of said gene.

25

52. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising:

comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of XM\_062147 or XM\_061676 with SEQ ID NOS 63 or 69 of claim 59.

30

53. A method of claim 52, wherein said polymorphism is a nucleotide deletion, substitution,

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inversion, or transposition.

54. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by XM\_062147 (SEQ ID NO 63) or XM\_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

55. A mammalian immune system cell whose genome comprises a functional disruption of a gene represented by XM\_062147 (SEQ ID NO 63) or XM\_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

10

56. A mammalian cell of claim 55, wherein said cell is a mouse cell.

57. A non-human, transgenic mammal, or a cell thereof, comprising a gene operatively linked to an expression control sequence effective to express said gene in immune system, wherein said sequence is SEQ ID NOS 65, 66, 71, 72, 73, 74, or 75.

15

58. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for XM\_062147 (SEQ ID NO 63 or 64) or XM\_061676 (SEQ ID NO 69 or 70) of claim 59, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

20

59. A composition comprising:

bone marrow specific genes consisting essentially of XM\_062147 (SEQ ID NO 63 or 64) and XM\_061676 (SEQ ID NO 69 or 70), or polypeptides thereof.

25

60. A method of detecting a kidney cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for a polynucleotide, or a naturally-occurring polymorphisms thereof, of claim 81 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

30

detecting specific hybridization.

61. A method of claim 60, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

5 RACE PCR, or *in situ* hybridization.

62. A method of detecting an kidney cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide  
coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof,

10 under conditions effective for said binding partner bind specifically to said polypeptide, and  
detecting specific binding.

63. A method of claim 62, wherein said detecting is performed by: immunocytochemistry,  
immunoprecipitation, or Western blot.

15

64. A method of delivering an agent to a kidney cell, comprising:

contacting a kidney cell with an agent coupled to binding partner specific for  
polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring  
polymorphism thereof, whereby said agent is delivered to said cell.

20

65. A method of claim 64, wherein the agent is a therapeutic agent, a cytotoxic agent, or an  
imaging agent.

66. A method of claim 64, wherein the binding partner is an antibody.

25

67. A method of modulating a kidney cell, comprising:

contacting said cell with an agent effective to modulate a polynucleotide, or  
polypeptide encoded thereby, or a naturally-occurring polymorphism thereof, of claim 81,  
whereby the kidney cell is modulated.

30

68. A method of assessing kidney function, comprising:

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detecting a polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of kidney function.

5 69. A method of claim 68, wherein said detecting is performed using an antibody which is specific for said polypeptide.

70. A method of claim 69, wherein said detecting is performed by RIA, ELISA, or Western blot.

10

71. A method of expressing a heterologous polynucleotide in kidney cells, comprising:  
expressing a nucleic acid construct in kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS. 106, 109, 110, 113, 114, 117, 118, 121,  
15 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151.

72. A method of diagnosing a kidney disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

20 assessing the expression of a polynucleotide of claim 81, or a polypeptide encoded thereby, or naturally-occurring polymorphisms thereof, in a tissue sample comprising kidney cells.

73. A method of claim 72, wherein assessing is:

25 measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

74. A method of assessing a therapeutic or preventative intervention in a subject having a kidney disease, comprising,

30 determining the expression levels of a polynucleotide of claim 81, a naturally-occurring polymorphism thereof, or polypeptide encoded thereby, in a tissue sample

comprising kidney cells.

75. A method of claim 74, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

5

76. A method for identifying an agent that modulates the expression of a polynucleotide or polypeptide selectively expressed in kidney cells, comprising,

contacting an kidney cell with a test agent under conditions effective for said test agent to modulate the expression of a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or the biological activity of a polypeptide encoded thereby, in said kidney cell, and

10

determining whether said test agent modulates said gene or polypeptide.

77. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

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78. A mammalian kidney cell whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

20

79. A mammalian cell of claim 78, wherein said cell is a mouse cell.

80. A method of selecting a gene predominantly expressed in kidney cells from a database comprising polynucleotide sequences for genes, comprising:

25



displaying, in a computer-readable medium, a polynucleotide sequence, or a polypeptide encoded thereby, of claim 81, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

5

81. A composition comprising two or more of the following polynucleotides expressed selectively in kidney:

TMD0049 (XM\_057351), TMD0190 (XM\_087157), TMD0242 (XM\_088369), TMD0335 (XM\_089960), TMD0371, TMD0374, TMD0469 (XM\_038736), TMD0719 (XM\_059548), TMD0731 (XM\_059703), TMD0785 (XM\_060310), TMD0841 (XM\_060623), TMD1114 (NM\_019841), and/or TMD 1148 (XM\_087108).

10

82. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, of claim 113 under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

15

83. A method of claim 82, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

20

84. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, of claim 113 under conditions effective for said binding partner bind specifically to said polypeptide, and, detecting specific binding.

25

85. A method of claim 84, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

30

86. A method of delivering an agent to a pancreas cell, comprising:

contacting a pancreas cell with an agent coupled to binding partner specific for

TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, of claim 113, whereby said agent is delivered to said cell.

87. A method of claim 86, wherein the agent is a therapeutic agent or an imaging agent.

5

88. A method of claim 86, wherein the agent is cytotoxic.

89. A method of claim 86, wherein the binding partner is an antibody.

10 90. A method of modulating a pancreas cell, comprising:

contacting said cell with an agent effective to modulate TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, or the biological activity of a polypeptide encoded thereby, of claim 113, whereby the pancreas cell is modulated.

15 91. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

20 92. A method of claim 91, wherein said detecting is performed using an antibody which is specific for said polypeptide.

93. A method of claim 91, wherein said detecting is performed by RIA, ELISA, or Western blot.

25

94. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 156-161, 166, 179, or 180.

30

95. A method of diagnosing a pancreas disease associated with abnormal gene expression,

or determining a subject's susceptibility to such disease, comprising:

assessing the expression of TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, or polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

5

96. A method of claim 95, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

10

97. A method of claim 95, wherein said assessing is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and  
using a polynucleotide probe having a sequence selected from SEQ ID NOS 154, 155,  
15 164, 165, 169, 170, 173, 174, 177, 178, or a complement thereto.

98. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas disease, comprising,

determining the expression levels of TMD0986, XM\_061780, XM\_061781,  
20 XM\_061784, or XM\_061785, or a polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

99. A method of claim 98, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

25

100. A method for identifying an agent that modulates the expression of TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785, or the biological activity of a polypeptide encoded thereby, comprising,

contacting a pancreas cell with a test agent under conditions effective for said test  
30 agent to modulate the expression of TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785 of claim 113, or the biological activity of a polypeptide encoded thereby, in said

pancreas cell, and

determining whether said test agent modulates said gene or polypeptide.

101. A method of claim 100, wherein said agent is an antisense polynucleotide to a target  
5 polynucleotide sequence selected from SEQ ID NO 152, 162, 167, 171, or 175 and which is  
effective to inhibit translation of said gene.

102. A method of detecting polymorphisms in TMD0986, XM\_061780, XM\_061781,  
XM\_061784, or XM\_061785, comprising,

10 comparing the structure of: genomic DNA or RNA or cDNA comprising all or part  
of an allele of TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785,  
with SEQ ID NOS 152, 153, 162, 163, 167, 168, 171, 172, 175, or 176 of claim 113.

103. A method of claim 102, wherein said polymorphism is a nucleotide deletion,  
15 substitution, inversion, or transposition.

104. A method of identifying a pancreatic disease or pancreatic disease-susceptibility,  
comprising:

determining the association of a pancreatic disease or pancreatic disease-susceptibility  
20 with a nucleotide sequence present within the pancreatic gene complex of claim 113.

105. A method of claim 104, wherein the pancreatic gene complex is from LOC160025-  
LOC119954.

106. A method of claim 104, wherein determining is performed by producing a human-  
25 linkage map of said complex.

107. A method of claim 104, wherein determining is performed by comparing the  
nucleotide sequences between normal subjects and subjects having a pancreas disorder.

30 108. A non-human, transgenic mammal whose genome comprises a functional disruption of  
a gene represented by TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785

of claim 113, and which has a defect in pancreas function.

109. A mammalian pancreas cell whose genome comprises a functional disruption of a gene represented by TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785 of claim

5 113, and which has a defect in pancreas function.

110. A mammalian cell of claim 109, wherein said cell is a mouse cell.

111. A pancreas cell, comprising a gene operatively linked to an expression control sequence  
10 effective to express said gene in pancreas, wherein said sequence is SEQ ID NOS 156-161,  
179, or 180.

112. A method of selecting a gene predominantly expressed in pancreas cells from a database comprising polynucleotide sequences for genes, comprising:

15 displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0986, XM\_061780, XM\_061781, XM\_061784, or XM\_061785 of claim 113, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

20

113. A composition comprising: a pancreas specific gene consisting essentially of TMD0986, XM\_061780, XM\_061781, XM\_061784, and/or XM\_061785, or a polypeptide encoded thereby.

25 114. An isolated polynucleotide comprising a polynucleotide sequence which codes without interruption for a human TMD0986 having an amino acid sequence set forth in SEQ ID NO 153, or a complement thereto.

115. An isolated polynucleotide comprising,

30 a human TMD0986 polynucleotide sequence having 90% or more nucleotide sequence identity to the polynucleotide sequence set forth in SEQ ID NO 152 along its entire

-144-

length, which codes without interruption for human TMD0986, or a complement thereto, and which has G-protein coupling activity.

116. An isolated human TMD0986 polypeptide comprising the amino acid sequence of a  
5 human TMD0986 as set forth in SEQ ID NO 153.

117. An isolated human TMD0986 polypeptide consisting essentially of amino acids 1-117  
of a human TMD0986 as set forth in SEQ ID NO 153.

10 118. An isolated polypeptide which is human TMD0986 having 90% or more amino acid  
sequence identity to the amino acid sequence set forth in SEQ ID NO 153, and which has  
protein binding activity.

15 119. An antibody specific for an epitope selected from the polypeptide of claim 117.

120. A method of detecting an retinal cell, comprising:  
contacting a sample comprising cells with a polynucleotide specific for NM\_013941  
(SEQ ID NO 181), or a naturally-occurring polymorphisms thereof, of claim 142 under  
conditions effective for said polynucleotide to hybridize specifically to said gene, and  
20 detecting specific hybridization.

121. A method of claim 120, wherein said detecting is performed by:  
Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,  
RACE PCR, or *in situ* hybridization.

25 122. A method of detecting an retinal cell, comprising:  
contacting a sample comprising cells with a binding partner specific for a polypeptide  
coded for by NM\_013941 (SEQ ID NO 182), or a naturally-occurring polymorphism thereof,  
of claim 142 under conditions effective for said binding partner bind specifically to said  
30 polypeptide, and  
detecting specific binding.

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123. A method of claim 122, wherein said detecting is performed by:  
immunocytochemistry, immunoprecipitation, or Western blot.

124. A method of delivering an agent to a retinal cell, comprising:

5       contacting a retinal cell with an agent coupled to binding partner specific for by  
NM\_013941 (SEQ ID NO 182), or naturally-occurring polymorphism thereof, of claim 142,  
whereby said agent is delivered to said cell.

125. A method of claim 124, wherein the agent is a therapeutic agent or an imaging agent.

10

126. A method of claim 124, wherein the agent is cytotoxic.

127. A method of claim 124, wherein the binding partner is an antibody.

15   128. A method of modulating a retinal cell, comprising:

      contacting said cell with an agent effective to modulate NM\_013941 (SEQ ID NO  
181 or 182), or the biological activity of a polypeptide encoded thereby, of claim 142,  
whereby the retinal cell is modulated.

20   129. A method of diagnosing a retinal disease associated with abnormal gene expression, or  
determining a subject's susceptibility to such disease, comprising:

      assessing the expression of NM\_013941, a polymorphism thereof, or polypeptide  
encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

25   130. A method of claim 129, wherein assessing is:

      measuring expression levels of said gene, determining the genomic structure of said  
gene, determining the mRNA structure of transcripts from said gene, or measuring the  
expression levels of polypeptide coded for by said gene.

30   131. A method of claim 129, wherein said assessing detecting is performed by:

      Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

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RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 183 or 184, or a complement thereto.

5 132. A method of assessing a therapeutic or preventative intervention in a subject having an retinal disease, comprising,

determining the expression levels of NM\_013941, a polymorphism thereof, or polypeptide encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

10 133. A method of claim 132, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

134. A method for identifying an agent that modulates the expression of NM\_013941 or the biological activity of a polypeptide encoded thereby, comprising,

15 contacting an retinal cell with a test agent under conditions effective for said test agent to modulate the expression of NM\_013941 or a polymorphism thereof, of claim 142, or the biological activity of a polypeptide encoded thereby, in said retinal cell, and determining whether said test agent modulates said gene or polypeptide.

20 135. A method of claim 134, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NO 181 and which is effective to inhibit translation of said gene.

136. A method of detecting polymorphisms in NM\_013941, comprising:

25 comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of NM\_013941, with SEQ ID NOS 181 or 182 of claim 142.

137. A method of claim 136, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

30 138. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by NM\_013941 (SEQ ID NO 181) of claim 142, and which has a defect in



retinal function.

139. A mammalian retinal cell whose genome comprises a functional disruption of a gene represented by NM\_013941 (SEQ ID NO 181) of claim 142, and which has a defect in retinal  
5 function.

140. A mammalian cell of claim 139, wherein said cell is a mouse cell.

141. A method of selecting a gene predominantly expressed in retinal cells from a database  
10 comprising polynucleotide sequences for genes, comprising:  
displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide  
sequence for NM\_013941 (SEQ ID NO 181 or 182) of claim 142, or complements to the  
polynucleotides sequence,  
wherein said displayed sequences have been retrieved from said database upon  
15 selection by a user.

142. A composition comprising:  
a retinal specific gene consisting essentially of NM\_013941 (SEQ ID NO 181 or  
182), or a polypeptide encoded thereby.

20 143. A method of detecting a spleen cell, comprising:  
contacting a sample comprising cells with a polynucleotide specific for TMD1030  
(XM\_166853) or TMD0621 (XM\_166205) of claim 170 under conditions effective for said  
polynucleotide to hybridize specifically to said gene, and  
25 detecting specific hybridization.

144. A method of claim 143, wherein said detecting is performed by:  
Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,  
RACE PCR, or *in situ* hybridization.

30 145. A method of detecting a spleen cell, comprising:  
contacting a sample comprising cells with a binding partner specific for a polypeptide

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coded for by TMD1030 (XM\_166853) or TMD0621 (XM\_166205) of claim 170 under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

5 146. A method of claim 145, wherein said detecting is performed by:  
immunocytochemistry, immunoprecipitation, or Western blot.

147. A method of delivering an agent to a spleen cell, comprising:  
contacting a spleen with an agent coupled to binding partner specific for TMD1030  
10 (XM\_166853) or TMD0621 (XM\_166205) of claim 170, whereby said agent is delivered to  
said cell.

148. A method of claim 147, wherein the agent is a therapeutic agent or an imaging agent.

15 149. A method of claim 148, wherein the agent is cytotoxic.

150. A method of claim 147, wherein the binding partner is an antibody.

151. A method of modulating a spleen, immune, or reticuloendothelial cell, comprising:  
20 contacting said cell with an agent effective to modulate TMD1030 (XM\_166853),  
TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), or the  
biological activity of a polypeptide encoded thereby, of claim 170, whereby the cell is  
modulated.

25 152. A method of assessing spleen function, comprising:  
detecting a polypeptide coded for by TMD1030 (XM\_166853) or TMD0621  
(XM\_166205) of claim 170, or fragments thereof, in a body fluid, whereby the amount of  
said polypeptide in said fluid is a measure of spleen function.

30 153. A method of claim 152, wherein said detecting is performed using an antibody which is  
specific for said polypeptide.

154. A method of claim 152, wherein said detecting is performed by RIA, ELISA, or Western blot.

5 155. A method of expressing a heterologous polynucleotide in spleen cells, comprising:  
expressing a nucleic acid construct in spleen cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NO 205-213.

10 156. A method of assessing a therapeutic or preventative intervention in a subject having a spleen or lymphoid disease, comprising,  
determining the expression levels of TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), or a polypeptide encoded thereby, of claim 170 in a tissue sample comprising spleen, lymphoid, or  
15 reticuloendothelial cells.

157. A method of claim 156, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

20 158. A method for identifying an agent that modulates the expression of TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), comprising,  
contacting a spleen, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD1030  
25 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), of claim 170, and  
determining whether said test agent modulates said gene.

30 159. A method of claim 158, wherein said agent is an antisense which is effective to inhibit translation of said gene.

160. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), comprising,

contacting a polypeptide coded for by TMD1030 (XM\_166853), TMD1029

5 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205) of claim 170, with a test agent under conditions effective for said test agent to modulate said polypeptide, and determining whether said test agent modulates said polypeptide.

161. A method of detecting polymorphisms in comprising, comparing the structure of :

10 genomic DNA or RNA or cDNA comprising all or part of an allele of TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205), with SEQ ID NOS 185, 187, 189, or 191 of claim 170.

162. A method of claim 161, wherein said polymorphism is a nucleotide deletion,

15 substitution, inversion, or transposition.

163. A method of identifying a genetic basis for a spleen, lymphoid, and/or

reticuloendothelial disease or disease-susceptibility, comprising: determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility with a

20 nucleotide sequence present in the gene complex of claim 170.

164. A method of claim 163, wherein determining is performed by producing a human-linkage map of said complex.

25 165. A method of claim 163, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having a spleen, lymphoid, and/or reticuloendothelial disease.

166. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a

30 functional disruption of a gene represented by TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205) of claim 170, and

which has a defect in spleen, lymphoid, and/or reticuloendothelial disease function.

167. A mammalian cell of claim 166, wherein said cell is a mouse cell.

5 168. A spleen, lymphoid, and/or reticuloendothelial cell, comprising a gene operatively linked to an expression control sequence effective to express said gene in spleen, lymphoid, and/or reticuloendothelial, wherein said sequence is SEQ ID NO 205-213.

169. A method of selecting a gene predominantly expressed in spleen, lymphoid, and/or  
10 reticuloendothelial cells from a database comprising polynucleotide sequences for genes, comprising:  
displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), or TMD0621 (XM\_166205) of claim 170, or complements to the  
15 polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

170. A composition consisting essentially of the 11q12.2 spleen gene complex, comprising  
TMD1030 (XM\_166853), TMD1029 (XM\_166854), TMD1028 (XM\_166855), and  
20 TMD0621 (XM\_166205).

171. A composition of claim 170, wherein said complex consists essentially of the chromosome region between STS markers G62658 and SHGC-154002.

25 172. A method of detecting a pancreas cell, comprising:  
contacting a sample comprising cells with a polynucleotide specific TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199  
30 under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization.

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173. A method of claim 172, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

5 174. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or

10 TMD1127

of claim 199 under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

15 175. A method of claim 174, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

176. A method of delivering an agent to a pancreas cell, comprising:

contacting a pancreas with an agent coupled to binding partner specific for

20 TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, whereby said agent is delivered to said cell.

25 177. A method of claim 176, wherein the agent is a therapeutic agent or an imaging agent.

178. A method of claim 176, wherein the agent is cytotoxic.

179. A method of claim 176, wherein the binding partner is an antibody.

30

180. A method of modulating a pancreas, immune, or reticuloendothelial cell, comprising:

contacting said cell with an agent effective to modulate TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or the biological activity of  
5 a polypeptide encoded thereby, of claim 199, whereby the cell is modulated.

181. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639,  
10 TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

182. A method of claim 181, wherein said detecting is performed using an antibody which is specific for said polypeptide.

15

183. A method of claim 181, wherein said detecting is performed by RIA, ELISA, or Western blot.

184. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

20 expressing a nucleic acid construct in pancreas cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 300, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344.

25

185. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas or lymphoid disease, comprising,

determining the expression levels of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639,  
30 TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or a polypeptide encoded thereby, of claim 199 in

a tissue sample comprising pancreas, lymphoid, or reticuloendothelial cells.

186. A method of claim 185, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

5

187. A method for identifying an agent that modulates the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

10

contacting a pancreas, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, and

15

determining whether said test agent modulates said gene.

188. A method of claim 187, wherein said agent is an antisense which is effective to inhibit translation of said gene.

20

189. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

25

contacting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, with a test agent under conditions effective for said test agent to modulate said polypeptide, and

30

determining whether said test agent modulates said polypeptide.



190. A method of claim 189, wherein said test agent is an antibody.

191. A method of detecting polymorphisms in comprising, comparing the structure of :  
genomic DNA or RNA or cDNA comprising all or part of an allele of

5 TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290,  
TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675,  
TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127,  
with SEQ ID NOS of Table 23 of claim 199.

10 192. A method of claim 191, wherein said polymorphism is a nucleotide deletion,  
substitution, inversion, or transposition.

193. A method of identifying a genetic basis for a pancreas disease or disease-susceptibility,  
comprising: determining the association of a pancreas disease or disease-susceptibility with a  
15 gene of claim 199.

194. A method of claim 193, wherein determining is performed by producing a human-  
linkage map of said gene.

20 195. A method of claim 193, wherein determining is performed by comparing the  
nucleotide sequences between normal subjects and subjects having a pancreas disease.

196. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a  
functional disruption of a gene represented by TMD0077, TMD0233, TMD0256, TMD0258,  
25 TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639,  
TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739,  
TMD0753, TMD1111, and/or TMD1127, of claim 199, and which has a defect in pancreas,  
lymphoid, and/or reticuloendothelial disease function.

30 197. A mammalian cell of claim 196, wherein said cell is a mouse cell.

198. A method of selecting a gene predominantly expressed in pancreas tissue from a

database comprising polynucleotide and amino acid sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

199. A composition comprising genes and/or polypeptide which are expressed

10 predominantly in pancreas tissue comprising:

TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127.

STS	RNA	Accn	locus	Gene code
35520K	RH79988 155920K			
35530K	SHGC-5451 155930K	XM_173381	LOC254079	
35940K	RH93848 155940K			
35950K	RH04X85 155940K	XM_086610	CD1D	
35960K	SHGC-82752 155950K			
35970K	D1S3312 155960K			
35980K	RH66323 155960K			
35990K				
36000K				
36110K	RH12951 156010K	XM_048792	CD1A	
36120K	D1S3259 156020K			
36130K	RH11438 156030K			
36140K				
36150K		NM_001765.1	CD1C	
36160K	D1S3359 156050K			
36170K				
36180K	DXS7690 156060K			
36190K				
36200K	SHGC-127956090K	NM_001764.1	CD1B	
36210K				
36220K	AL009528 156110K	NM_030893.1	CD1E	
36230K	RH70821 156120K			
36240K	RH6963 156130K			
36250K				
36260K	SHGC-61823 156140K	XM_060945	LOC128360	TMD0024
36270K				
36280K		XM_060946	LOC128361	TMD1779
36290K				
36300K		XM_060947	LOC128362	TMD0884
36310K				
36320K		XM_060948	LOC128363	TMD0025
36330K	SHGC-155256220K			
36340K	SHGC-155256230K			
36350K		XM_089422	LOC164169	TMD1780
36360K				
36370K		XM_089421	LOC149631	TMD1781
36380K				
36390K		XM_060949	LOC128364	
36400K		XM_089420	LOC164168	
36410K				
36420K		XM_060950	LOC128365	
36430K				
36440K		XM_060951	LOC128366	
36450K	D1S3249 156350K			
36460K	G15944 156360K			
36470K	GDB:1918196360K	XM_060952	LOC128367	
36480K	GDB:1964786370K			
36490K	RH60459 156370K			
36500K	RH102597150300K	XM_060953	LOC128368	
36510K	RH69635 156380K			
36520K	RH65132 156390K			
36530K		NM_003126.1	SPTA1	
36540K				
36550K				
36560K	GDB:181553 156400K			
36570K				
36580K	RH118729 156410K			
36590K		XM_060954	LOC128369	
36600K				
36610K		XM_060955	LOC128370	
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Fig. 1

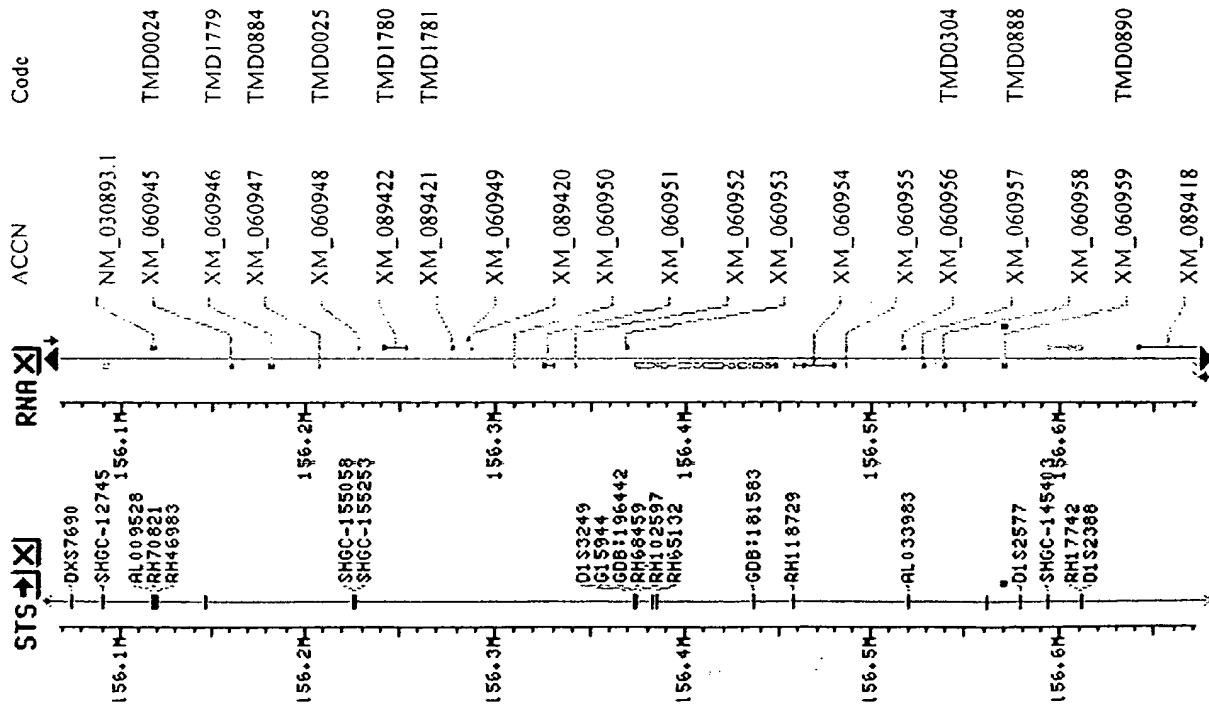


Fig. 2

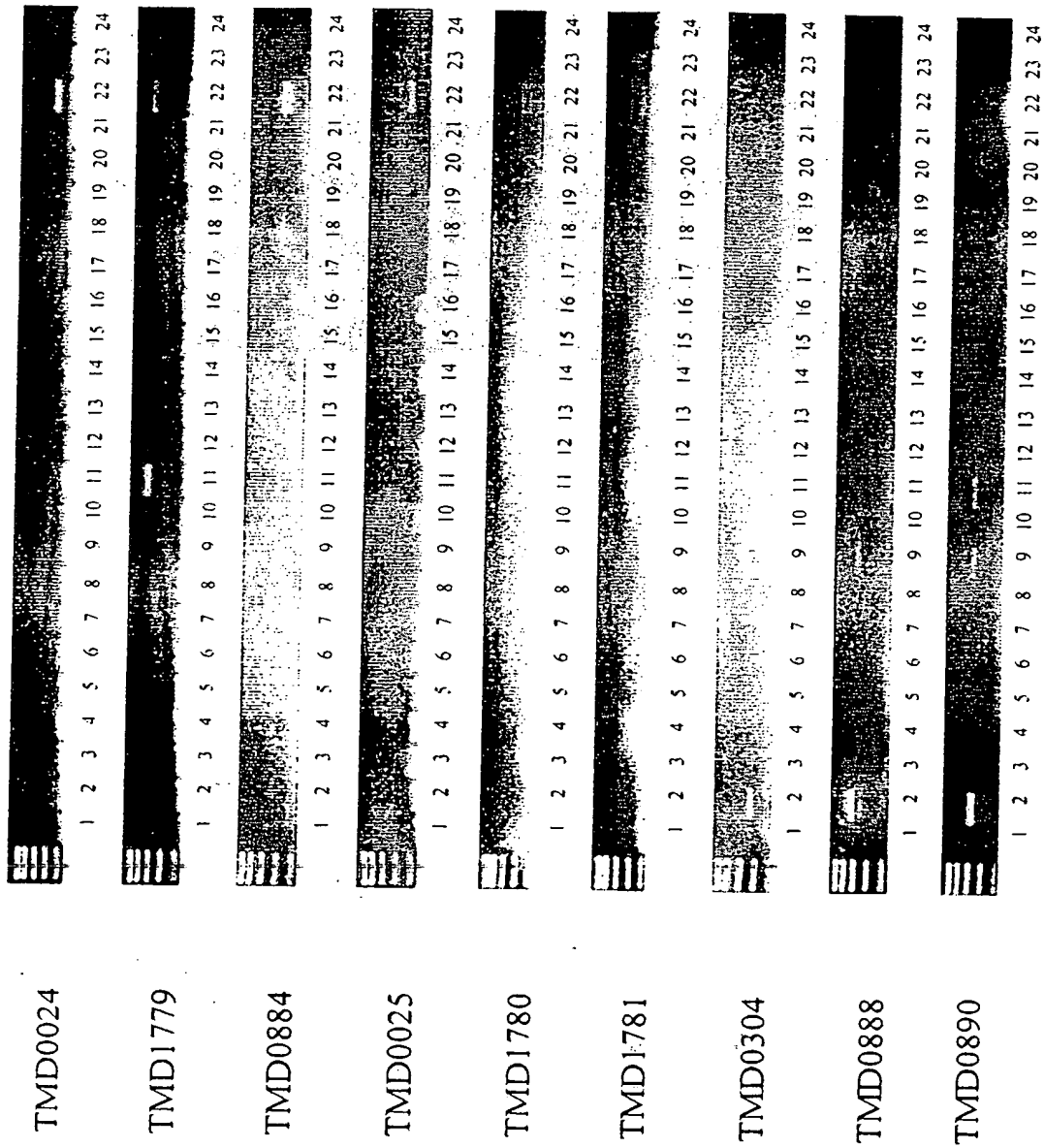
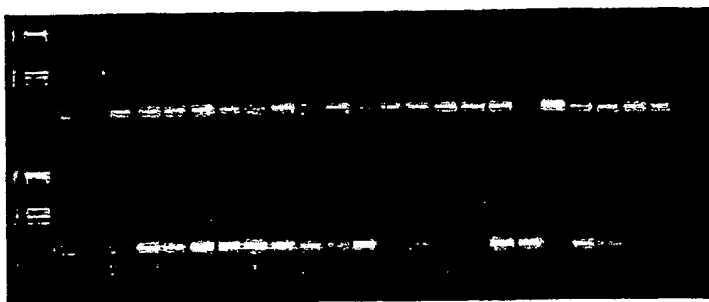


Fig. 3

XM\_062147



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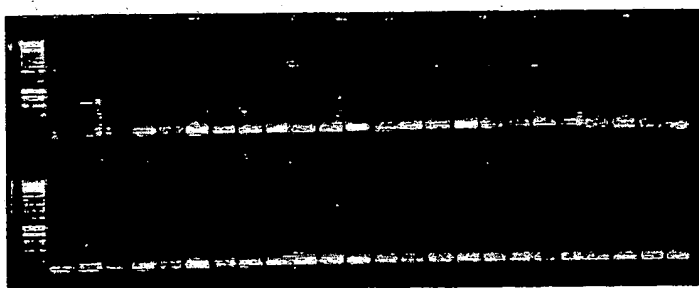


FIG. 4

Fig. 5a

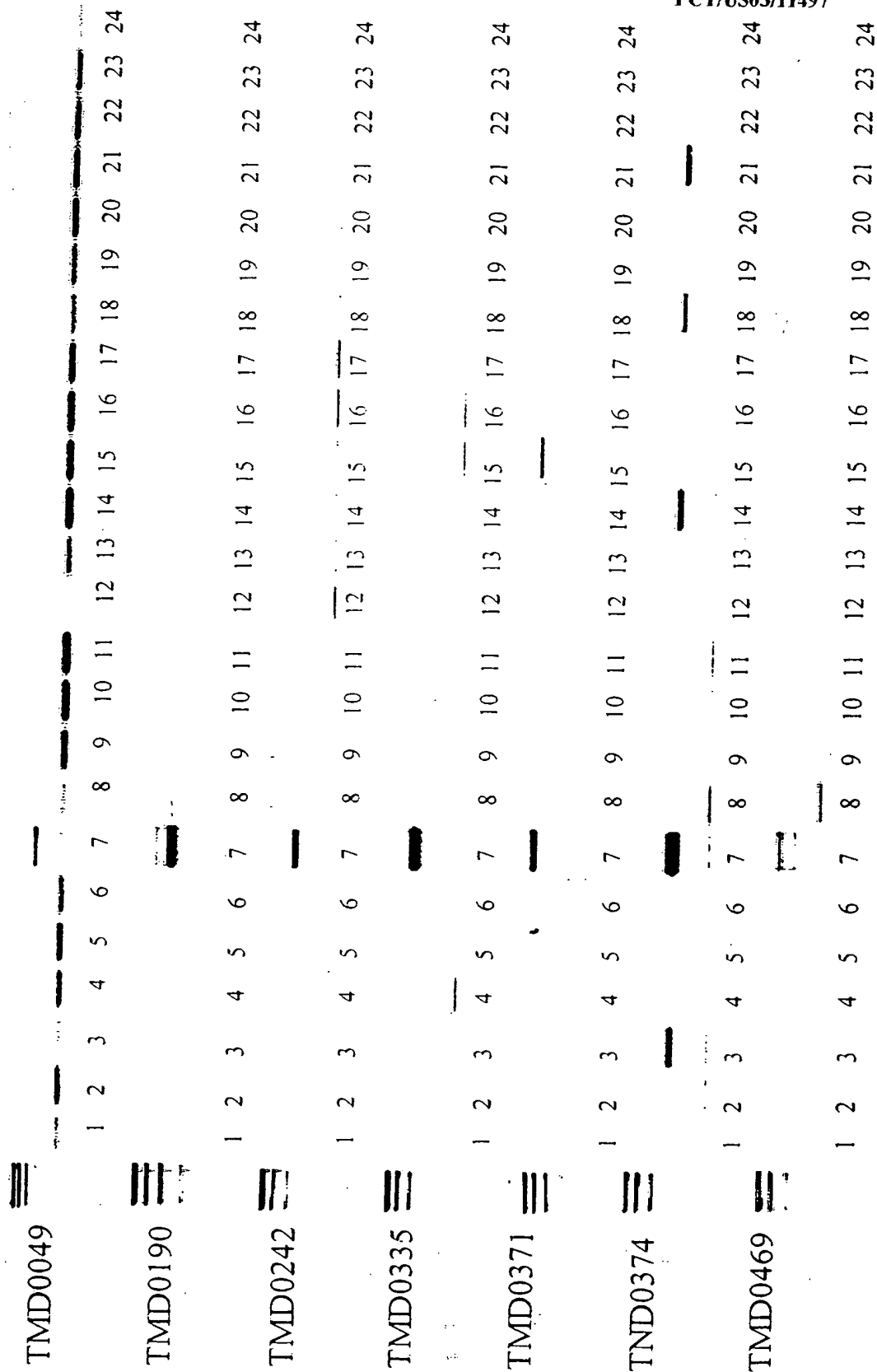


Fig. 5b





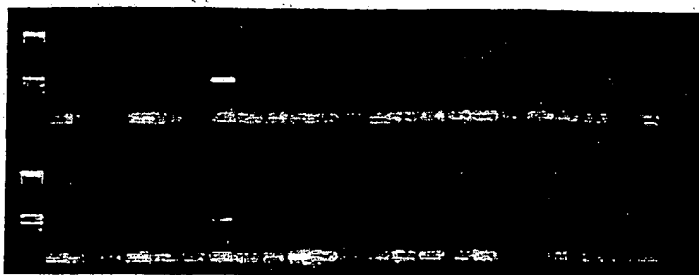


Fig. 6

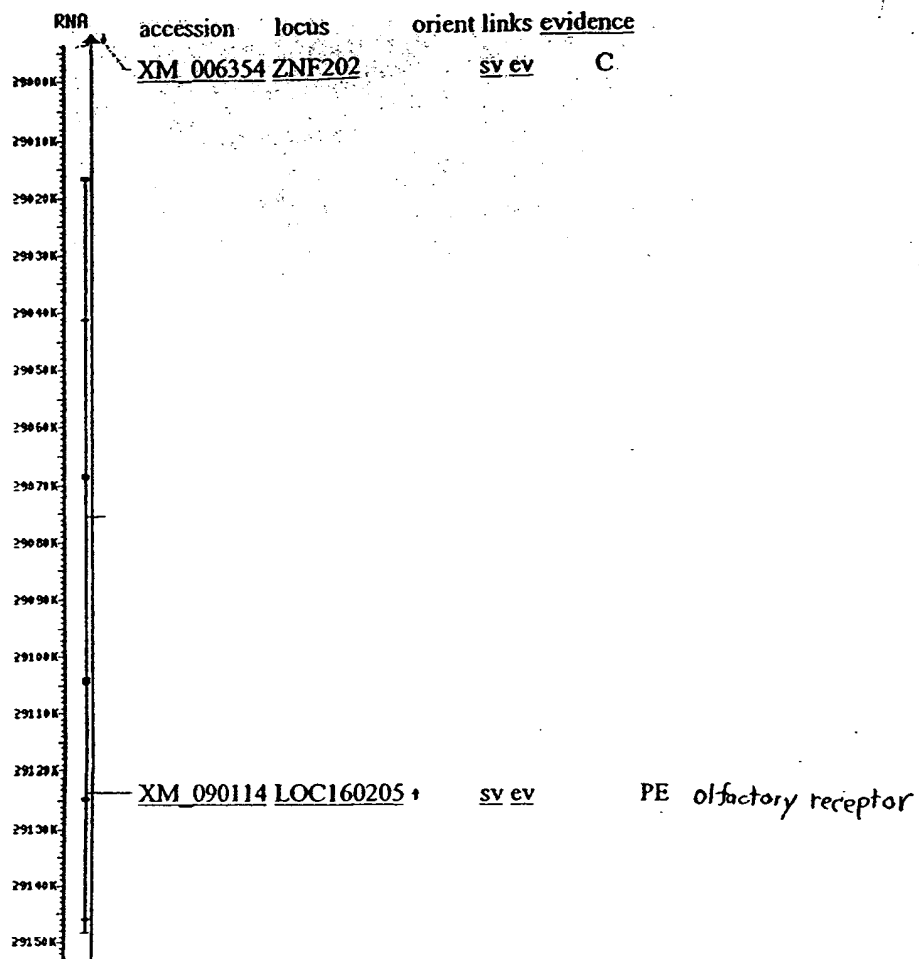


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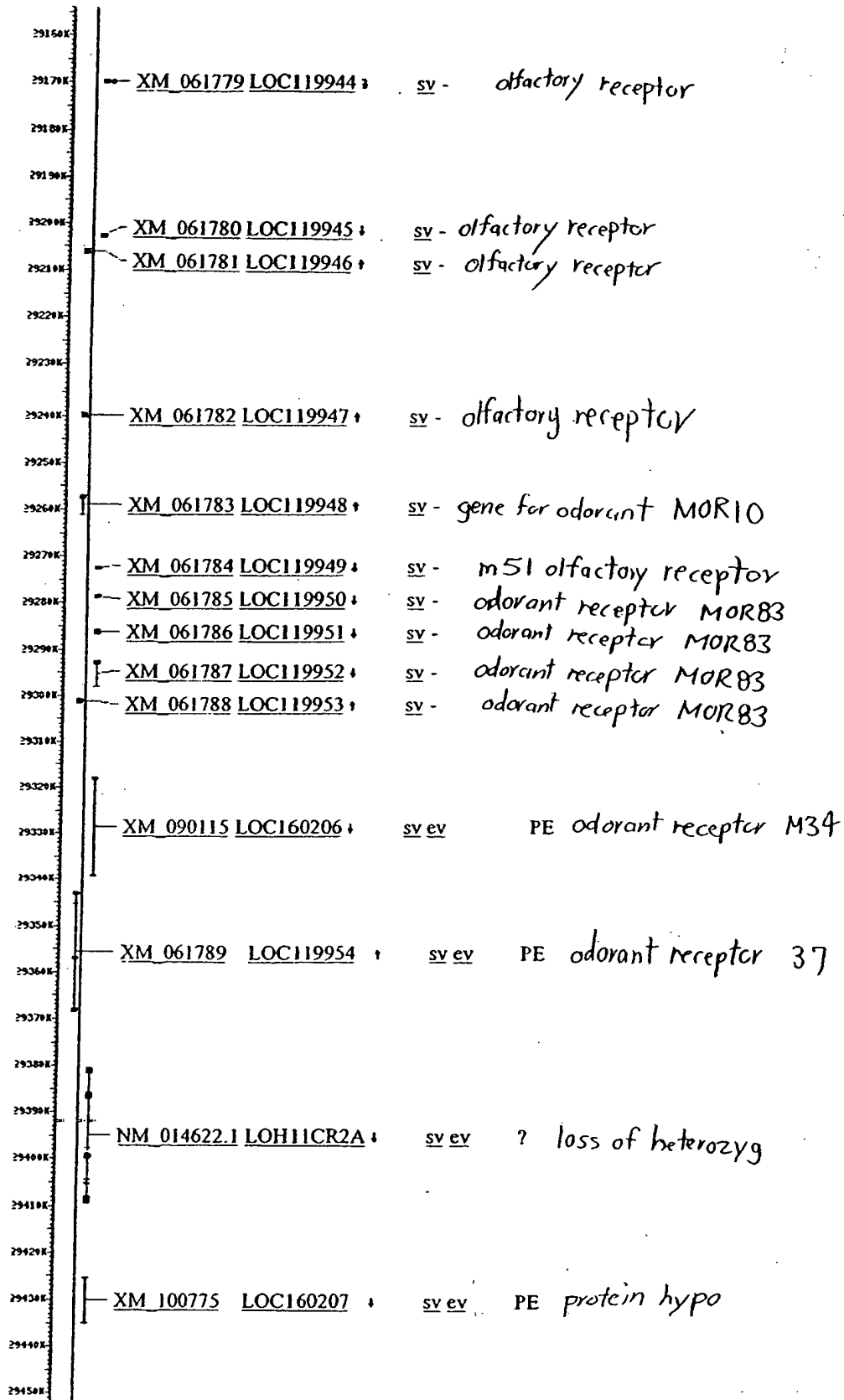


Fig 1B

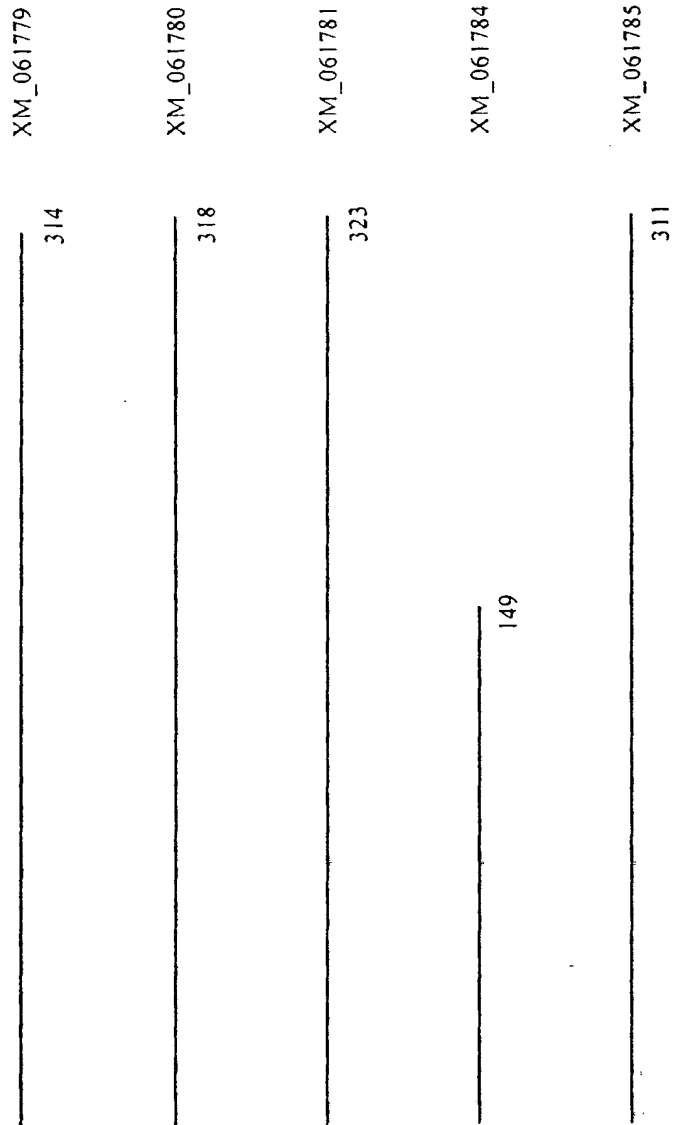
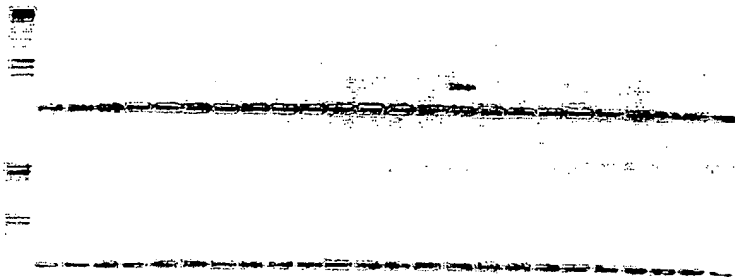
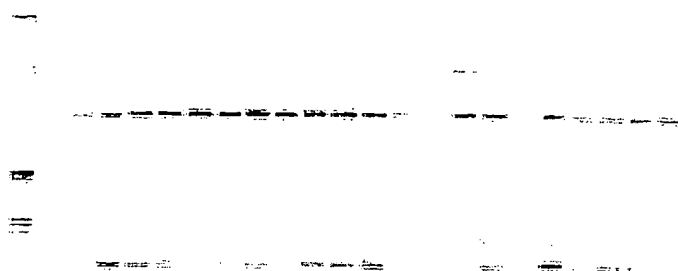


Fig. 8

XM\_061779



XM\_061780



XM\_061781

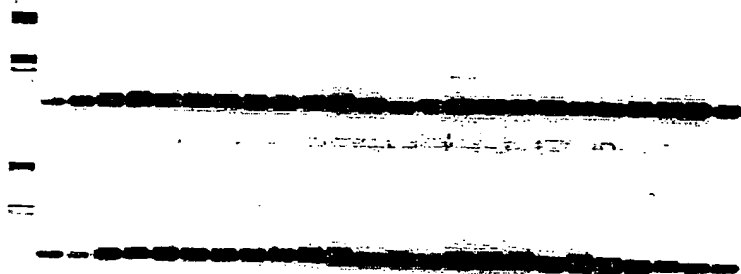
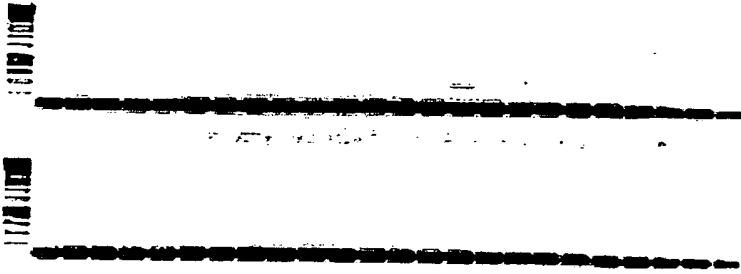


Fig. 9A

XM\_061784



XM\_061785

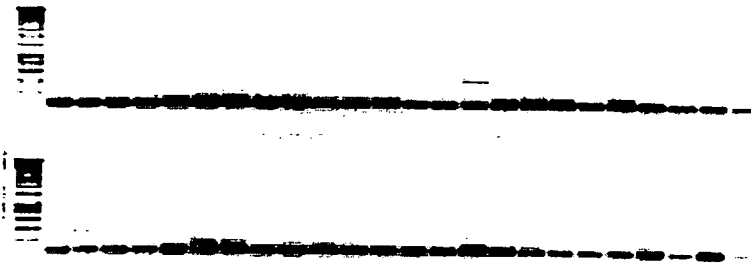


Fig. 9B

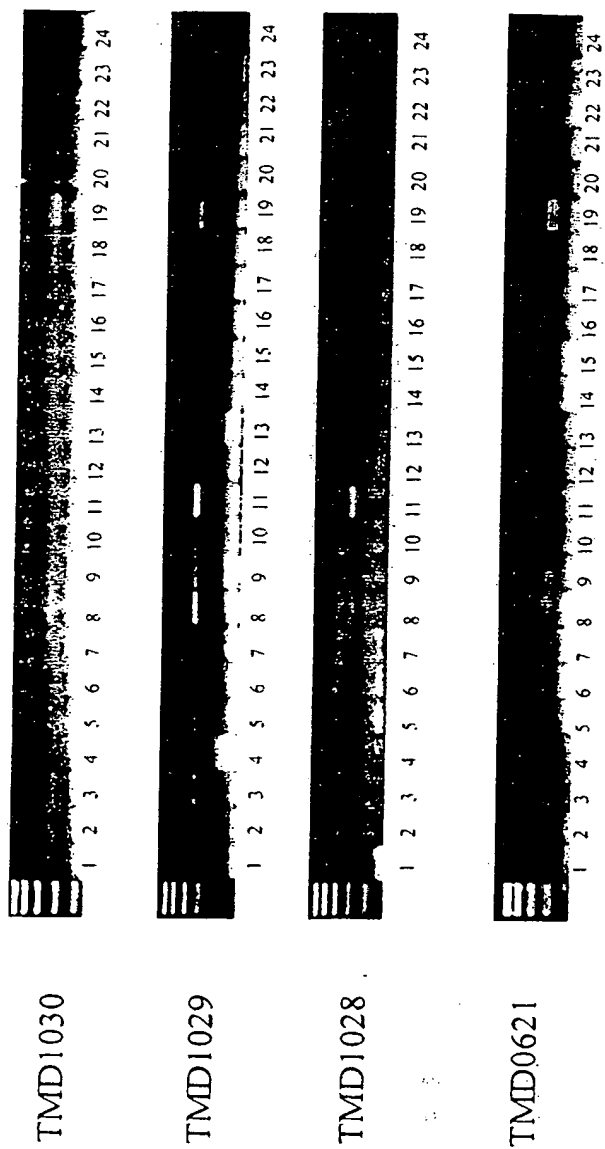


Fig.10

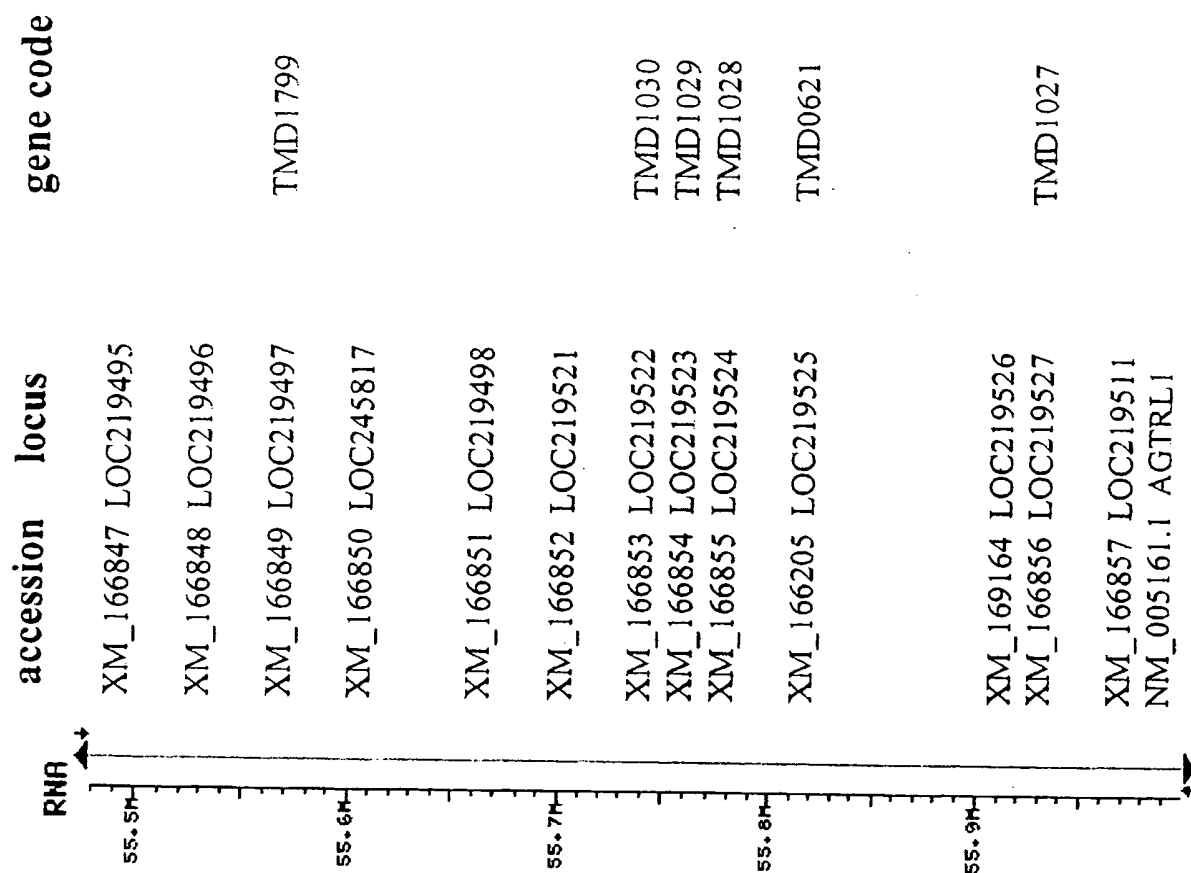


Fig. 11



FIG. 12A

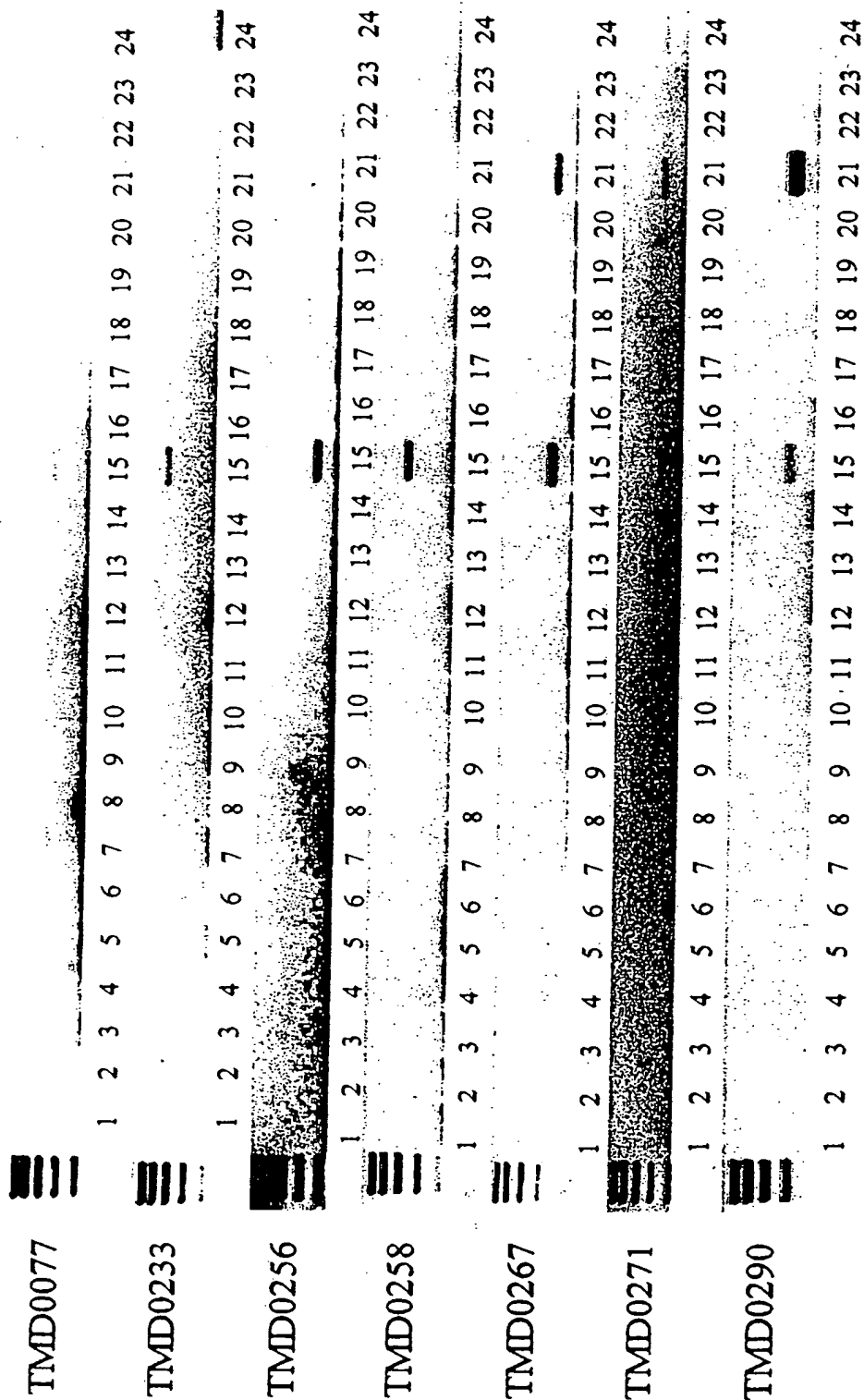


FIG. 12B

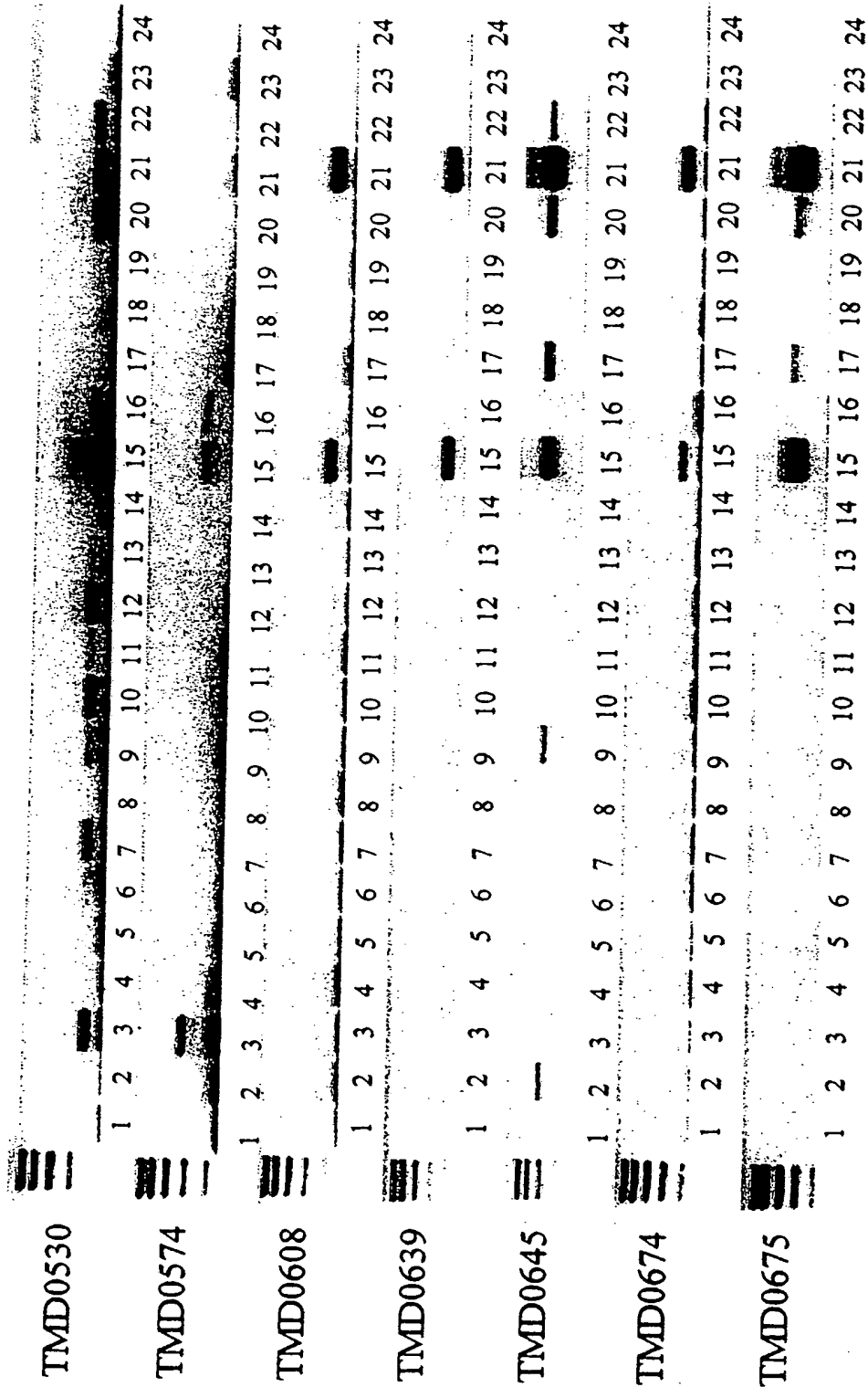
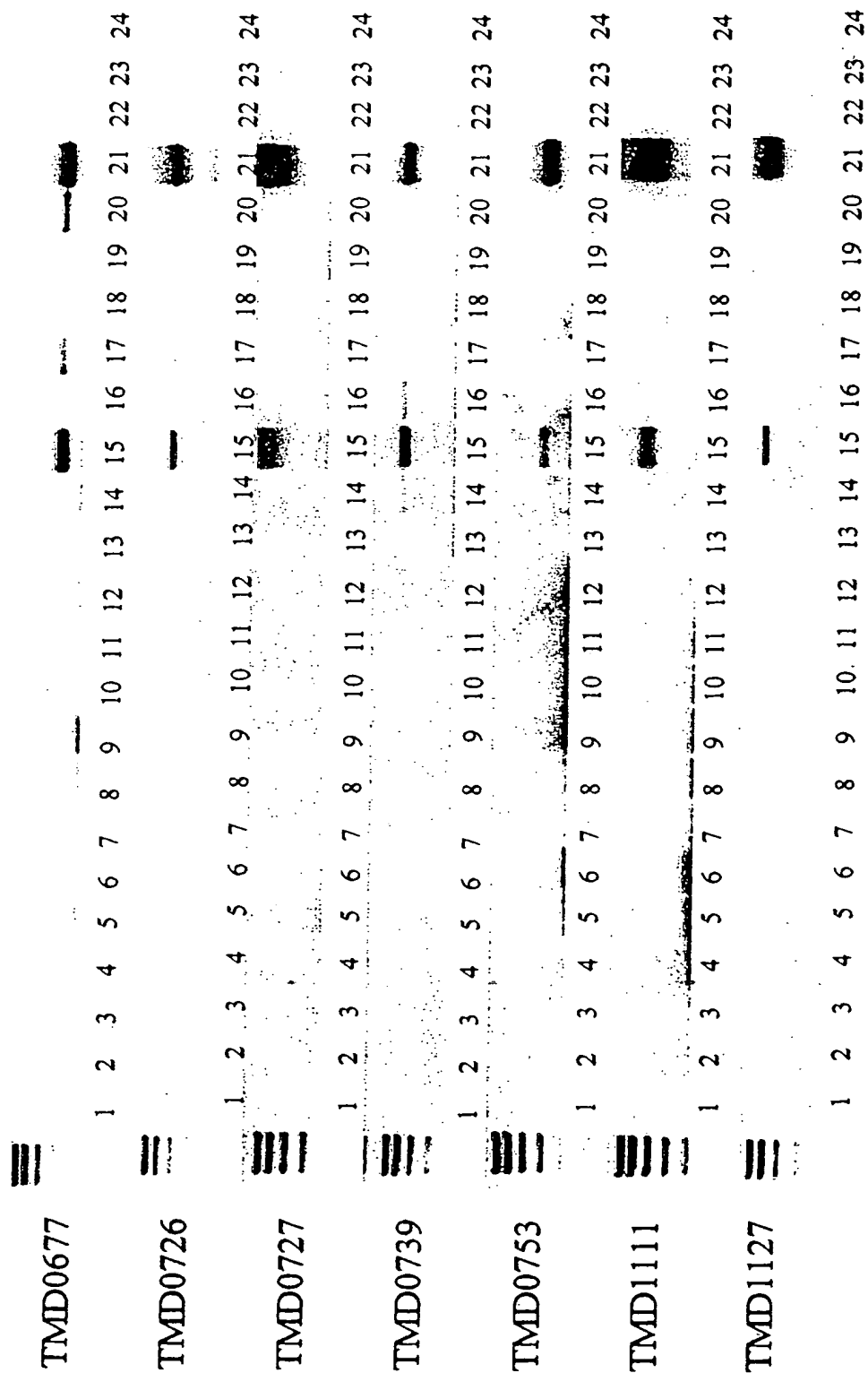


FIG. 12C



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Leu Gly Thr Asn Ala Ile Ile Ile Ser Thr Ile Val Leu Asp Arg Ala	50
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ctt cat act ccc atg tac ttc ttc ctt gcc atc ctt tct tgc tct gag	2228
Leu His Thr Pro Met Tyr Phe Phe Leu Ala Ile Leu Ser Cys Ser Glu	70
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Ile Cys Tyr Thr Phe Val Ile Val Pro Lys Met Leu Val Asp Leu Leu	85
75	80
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Ser Gln Lys Lys Thr Ile Ser Phe Leu Gly Cys Ala Ile Gln Met Phe	100
90	95
tcc ttc ctc ttc ttt ggc tcc tct cac tcc ttc ctg ctg gca gcc atg	2372
Ser Phe Leu Phe Phe Gly Ser Ser His Ser Phe Leu Leu Ala Ala Met	115
105	110
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Gly Tyr Asp Arg Tyr Met Ala Ile Cys Asn Pro Leu Arg Tyr Ser Val	130
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Cys Gly Phe Thr Val Ser Leu Val Thr Thr Ser Leu Val Phe His Leu	165
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Pro Phe His Ser Ser Asn Gln Leu His His Phe Phe Cys Asp Ile Ser	180
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Pro Val Leu Lys Leu Ala Ser Gln His Ser Gly Phe Ser Gln Leu Val	195
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215	220
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Ser Val Gly Arg Tyr Lys Thr Phe Ser Thr Cys Ala Ser His Leu Ile	245
235	240
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Val Val Thr Val His Tyr Ser Cys Ala Ser Phe Ile Tyr Leu Arg Pro	260
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275

265                      270

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4982

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 35              40              45

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 50              55              60

Ile Leu Ser Cys Ser Glu Ile Cys Tyr Thr Phe Val Ile Val Pro Lys
 65              70              75              80

Met Leu Val Asp Leu Leu Ser Gln Lys Lys Thr Ile Ser Phe Leu Gly
 85              90              95

Cys Ala Ile Gln Met Phe Ser Phe Leu Phe Phe Gly Ser Ser His Ser
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Phe Leu Leu Ala Ala Met Gly Tyr Asp Arg Tyr Met Ala Ile Cys Asn
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Pro Leu Arg Tyr Ser Val Leu Met Gly His Gly Val Cys Met Gly Leu
130              135              140

Met Ala Ala Ala Cys Ala Cys Gly Phe Thr Val Ser Leu Val Thr Thr
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Ser Leu Val Phe His Leu Pro Phe His Ser Ser Asn Gln Leu His His
165              170              175

Phe Phe Cys Asp Ile Ser Pro Val Leu Lys Leu Ala Ser Gln His Ser
180              185              190

Gly Phe Ser Gln Leu Val Ile Phe Met Leu Gly Val Phe Ala Leu Val
195              200              205

Ile Pro Leu Leu Leu Ile Leu Val Ser Tyr Ile Arg Ile Ile Ser Ala
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Phe Ile Tyr Leu Arg Pro Lys Thr Asn Tyr Thr Ser Ser Gln Asp Thr
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Leu Ile Ser Val Ser Tyr Thr Ile Leu Thr Pro Leu Phe Asn Pro Met  
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Leu Phe Ser Met Phe Pro His Ala His Arg Gly Gly Leu Leu Phe Phe	20	25	30	
att ccc ttg ctt ctc atc tac gga ttt atc cta act gga aac cta ata				144
Ile Pro Leu Leu Leu Ile Tyr Gly Phe Ile Leu Thr Gly Asn Leu Ile	35	40	45	
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Met Phe Ile Val Ile Gln Val Gly Met Ala Leu His Thr Pro Leu Tyr	50	55	60	
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Phe Phe Ile Ser Val Leu Ser Phe Leu Glu Ile Cys Tyr Thr Thr Thr	65	70	75	80
acc atc ccc aag atg ctg tcc tgc cta atc agt gag cag aag agc att				288
Thr Ile Pro Lys Met Leu Ser Cys Leu Ile Ser Glu Gln Lys Ser Ile	85	90	95	
tcc gtg gct ggc tgc ctc ctg cag atg tac ttt ttc cac tca ctt ggt				336
Ser Val Ala Gly Cys Leu Leu Gln Met Tyr Phe Phe His Ser Leu Gly	100	105	110	
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Ile Thr Glu Ser Cys Val Leu Thr Ala Met Ala Ile Asp Arg Tyr Ile	115	120	125	
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Ala Ile Cys Asn Pro Leu Arg Tyr Pro Thr Ile Met Ile Pro Lys Leu	130	135	140	
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Cys Ile Gln Leu Thr Val Gly Ser Cys Phe Cys Gly Phe Leu Leu Val	145	150	155	160
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Leu Pro Glu Ile Ala Trp Ile Ser Thr Leu Pro Phe Cys Gly Ser Asn	165	170	175	
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Gln Ile His Gln Ile Phe Cys Asp Phe Thr Pro Val Leu Ser Leu Ala	180	185	190	
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Cys Thr Asp Thr Phe Leu Val Val Ile Val Asp Ala Ile His Ala Ala	195	200	205	
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Glu Ile Val Ala Ser Phe Leu Val Ile Ala Leu Ser Tyr Ile Arg Ile	210	215	220	
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Ile Ile Val Ile Leu Gly Met His Ser Ala Glu Gly His His Lys Ala	225	230	235	240
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Phe Ser Thr Cys Ala Ala His Leu Ala Val Phe Leu Leu Phe Phe Gly	245	250	255	
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Ser Val Ala Val Met Tyr Leu Arg Phe Ser Ala Thr Tyr Ser Val Phe	260	265	270	
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Trp Asp Thr Ala Ile Ala Val Thr Phe Val Ile Leu Ala Pro Phe Phe	275	280	285	
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Asn Pro Ile Ile Tyr Ser Leu Lys Asn Lys Asp Met Lys Glu Ala Ile	290	295	300	
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Met Phe Ile Val Ile Gln Val Gly Met Ala Leu His Thr Pro Leu Tyr  
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Phe Phe Ile Ser Val Leu Ser Phe Leu Glu Ile Cys Tyr Thr Thr Thr  
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Thr Ile Pro Lys Met Leu Ser Cys Leu Ile Ser Glu Gln Lys Ser Ile  
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Ser Val Ala Gly Cys Leu Leu Gln Met Tyr Phe Phe His Ser Leu Gly  
 100 105 110

Ile Thr Glu Ser Cys Val Leu Thr Ala Met Ala Ile Asp Arg Tyr Ile  
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Ala Ile Cys Asn Pro Leu Arg Tyr Pro Thr Ile Met Ile Pro Lys Leu  
 130 135 140

Cys Ile Gln Leu Thr Val Gly Ser Cys Phe Cys Gly Phe Leu Leu Val  
 145 150 155 160

Leu Pro Glu Ile Ala Trp Ile Ser Thr Leu Pro Phe Cys Gly Ser Asn  
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Gln Ile His Gln Ile Phe Cys Asp Phe Thr Pro Val Leu Ser Leu Ala  
 180 185 190

Cys Thr Asp Thr Phe Leu Val Val Ile Val Asp Ala Ile His Ala Ala  
 195 200 205

Glu Ile Val Ala Ser Phe Leu Val Ile Ala Leu Ser Tyr Ile Arg Ile  
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Ile Ile Val Ile Leu Gly Met His Ser Ala Glu Gly His His Lys Ala  
 225 230 235 240

Phe Ser Thr Cys Ala Ala His Leu Ala Val Phe Leu Leu Phe Phe Gly  
 245 250 255

Ser Val Ala Val Met Tyr Leu Arg Phe Ser Ala Thr Tyr Ser Val Phe  
 260 265 270

Trp Asp Thr Ala Ile Ala Val Thr Phe Val Ile Leu Ala Pro Phe Phe  
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16U 200 PCT FINAL.ST25

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cac act cct atg tac ttc ttc ctc ttt gtc ctt tca tgt tct gaa acc 192  
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 Cys Tyr Thr Leu Val Ile Val Pro Lys Met Leu Thr Asn Leu Leu Ser  
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 Ala Ile Pro Thr Ile Ser Phe Ser Gly Cys Val Val Gln Leu Tyr Leu  
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 His Phe Phe Cys Asp Ile Ser Pro Val Ile Lys Leu Gly Cys Thr Asp  
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 180 185 190

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 Thr Cys Ala Ser His Leu Thr Val Val Val Val His Tyr Gly Cys Ala  
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 260 265 270

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Cys Tyr Thr Leu Val Ile Val Pro Lys Met Leu Thr Asn Leu Leu Ser  
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Phe Val Gly Leu Ala Cys Thr Asn Cys Phe Leu Ile Ala Val Met Gly  
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Asn Ile Leu Val Phe Ser Val Leu Leu Cys Ala Ser Asn Arg Ile Asn  
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His Phe Phe Cys Asp Ile Ser Pro Val Ile Lys Leu Gly Cys Thr Asp  
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Thr Asn Leu Lys Glu Met Val Ile Phe Phe Leu Ser Ile Leu Val Leu  
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Leu Val Pro Leu Val Leu Ile Phe Ile Ser Tyr Ile Phe Ile Val Ser  
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Leu Ile Tyr Leu Met Thr Val Leu Gly Asn Leu Leu Ile Phe Leu Val  
 35 40 45

Val Cys Leu Asp Ser Arg Leu His Thr Pro Met Tyr His Phe Val Ser  
 50 55 60

Ile Leu Ser Phe Ser Glu Leu Gly Tyr Thr Ala Ala Thr Ile Pro Lys  
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Met Leu Ala Asn Leu Leu Ser Glu Lys Lys Thr Ile Ser Phe Ser Gly  
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Cys Leu Leu Gln Ile Tyr Phe Phe His Ser Leu Gly Ala Thr Glu Cys  
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Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Leu Ala Ile Cys Arg  
 115 120 125

Pro Leu His Tyr Pro Thr Leu Met Thr Pro Thr Leu Cys Ala Glu Ile  
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160 200 PCT FINAL.ST25

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Cys Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser
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Tyr Val Phe His Ser Leu Gly Met Thr Glu Cys Tyr Leu Leu Gly Val
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225 230 235

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Pro Gly Ser Arg Pro Glu Ser Thr Asp Lys Leu Val Ala Leu Val Tyr
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&lt;213&gt; Homo sapiens

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Arg Cys Gly Met Ser Ala Pro Gln Cys Pro Cys Cys Cys Thr Pro Cys  
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Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser Tyr  
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Ala Gly Phe Ser Ala Ala Leu Val Pro Ala Thr Leu Thr Ala Thr Leu  
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192

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336

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Cys Asp Ile Ser Pro Val Ile Arg Leu Ala Cys Ala Asp Ser Tyr Ile  
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 35 40 45

His Thr Pro Met Tyr Phe Phe Leu Gly Ile Leu Ser Thr Ser Glu Thr  
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Phe Tyr Thr Phe Val Ile Leu Pro Lys Met Leu Ile Asn Leu Leu Ser  
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Val Ala Arg Thr Ile Ser Phe Asn Cys Cys Ala Leu Gln Met Phe Phe  
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Phe Leu Gly Phe Ala Ile Thr Asn Cys Leu Leu Leu Gly Val Met Gly  
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Tyr Asp Arg Tyr Ala Ala Ile Cys His Pro Leu His Tyr Pro Thr Leu  
 115 120 125

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Gly Phe Leu Ala Ser Leu Thr Val Val Asn Leu Val Phe Ser Leu Pro  
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Phe Ile Cys Gly Val Leu Val Leu Val Val Pro Phe Leu Phe Ile Cys  
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Val Ile Val His Tyr Gly Cys Ala Ser Phe Ile Tyr Leu Arg Pro Thr  
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Ala Asn Tyr Val Ser Asn Lys Asp Arg Leu Val Thr Val Thr Tyr Thr  
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275 280 285

Asp Val Gln Leu Ala Ile Arg Lys Val Leu Gly Lys Lys Gly Ile Leu  
290 295 300

Ser Ile Ser Glu Ile Phe Tyr Thr Thr Val Ile Leu Pro Lys Met Leu  
305 310 315 320

Ile Asn Leu Phe Ser Val Phe Arg Thr Leu Ser Phe Val Ser Cys Ala  
325 330 335

Thr Gln Met Phe Phe Phe Leu Gly Phe Ala Val Thr Asn Cys Leu Leu  
340 345 350

Leu Gly Val Met Gly Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu  
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Gln Tyr Ala Val Leu Met Ser Trp Arg Val Cys Gly Gln Leu Ile Ala  
370 375 380

Thr Cys Ile Ile Ser Gly Phe Leu Ile Ser Leu Val Gly Thr Thr Phe  
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Val Phe Ser Leu Pro Phe Cys Gly Ser Asn Lys Val Asn His Tyr Phe  
405 410 415

Cys Asp Ile Ser Pro Val Ile Arg Leu Ala Cys Ala Asp Ser Tyr Ile  
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Ser Glu Leu Val Ile Phe Ile Phe Gly Val Leu Val Leu Val Val Pro  
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Ala Ser Val Phe Tyr Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile	
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Lys Met Leu Val Asn Leu Val Val Lys Asp Arg Thr Ile Ser Phe Leu  
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Gly Cys Val Val Gln Phe Phe Phe Phe Cys Thr Phe Val Val Thr Glu  
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245 16U 200 PCT FINAL.ST25  
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ggaagagaat tcccaggagc c atg tca gcc tcc aat atc acc tta aca cat	1851
Met Ser Ala Ser Asn Ile Thr Leu Thr His	
1 5 10	
cca act gcc ttc ttg ttg gtg ggg att cca ggc ctg gaa cac ctg cac	1899
Pro Thr Ala Phe Leu Leu Val Gly Ile Pro Gly Leu Glu His Leu His	
15 20 25	
atc tgg atc tcc atc cct ttc tgc tta gca tat aca ctg gcc ctg ctt	1947
Ile Trp Ile Ser Ile Pro Phe Cys Leu Ala Tyr Thr Leu Ala Leu Leu	
30 35 40	
gga aac tgc act ctc ctt ctc atc atc cag gct gat gca gcc ctc cat	1995
Gly Asn Cys Thr Leu Leu Leu Ile Ile Gln Ala Asp Ala Ala Leu His	
45 50 55	
gaa ccc atg tac ctc ttt ctg gcc atg ttg gca gcc atc gac ctg gtc	2043
Glu Pro Met Tyr Leu Phe Leu Ala Met Leu Ala Ala Ile Asp Leu Val	
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ctt tcc tcc tca gca ctg ccc aaa atg ctt gcc ata ttc tgg ttc agg	2091
Leu Ser Ser Ser Ala Leu Pro Lys Met Leu Ala Ile Phe Trp Phe Arg	
75 80 85 90	
gat cgg gag ata aac ttc ttt gcc tgt ctg gcc cag atg ttc ttc ctt	2139
Asp Arg Glu Ile Asn Phe Phe Ala Cys Leu Ala Gln Met Phe Phe Leu	
95 100 105	
cac tcc ttc tcc atc atg gag tca gca gtg ctg ctg gcc atg gcc ttt	2187
His Ser Phe Ser Ile Met Glu Ser Ala Val Leu Leu Ala Met Ala Phe	
110 115 120	

16U 200 PCT FINAL.ST25

gac cgc tat gtg gct atc tgc aag cca ctg cac tac acc aag gtc ctg 2235  
 Asp Arg Tyr Val Ala Ile Cys Lys Pro Leu His Tyr Thr Lys Val Leu  
 125 130 135

act ggg tcc ctc atc acc aag att ggc atg gct gct gtg gcc cgg gct 2283  
 Thr Gly Ser Leu Ile Thr Lys Ile Gly Met Ala Ala Val Ala Arg Ala  
 140 145 150

gtg aca cta atg act cca ctc ccc ttc ctg ctg aga tgt ttc cac tac 2331  
 Val Thr Leu Met Thr Pro Leu Pro Phe Leu Leu Arg Cys Phe His Tyr  
 155 160 165 170

tgc cga ggc cca gtg atc gct cac tgc tac tgt gaa cac atg gct gtg 2379  
 Cys Arg Gly Pro Val Ile Ala His Cys Tyr Cys Glu His Met Ala Val  
 175 180 185

gtg agg ctg gcg tgt ggg gac act agc ttc aac aat atc tat ggc atc 2427  
 Val Arg Leu Ala Cys Gly Asp Thr Ser Phe Asn Asn Ile Tyr Gly Ile  
 190 195 200

gct gtg gcc atg ttt att gtg gtg ttg gac ctg ctc ctt gtt atc ctg 2475  
 Ala Val Ala Met Phe Ile Val Val Leu Asp Leu Leu Leu Val Ile Leu  
 205 210 215

tct tat atc ttt att ctt cag gca gtt cta ctg ctt gcc tct cag gag 2523  
 Ser Tyr Ile Phe Ile Leu Gln Ala Val Leu Leu Leu Ala Ser Gln Glu  
 220 225 230

gcc cac tac aag gca ttt ggg aca tgt gtc tct cat ata ggt gcc atc 2571  
 Ala His Tyr Lys Ala Phe Gly Thr Cys Val Ser His Ile Gly Ala Ile  
 235 240 245 250

tta gcc ttc tac aca act gtg gtc atc tct tca gtc atg cac cgt gta 2619  
 Leu Ala Phe Tyr Thr Thr Val Val Ile Ser Ser Val Met His Arg Val  
 255 260 265

gcc cgc cat gct gcc cct cat gtc cac atc ctc ctt gcc aat ttc tat 2667  
 Ala Arg His Ala Ala Pro His Val His Ile Leu Leu Ala Asn Phe Tyr  
 270 275 280

ctg ctc ttc cca ccc atg gtc aat ccc ata atc tat ggt gtc aag acc 2715  
 Leu Leu Phe Pro Pro Met Val Asn Pro Ile Ile Tyr Gly Val Lys Thr  
 285 290 295

aag caa atc cgt gag agc atc ttg gga gta ttc cca aga aag gat atg 2763  
 Lys Gln Ile Arg Glu Ser Ile Leu Gly Val Phe Pro Arg Lys Asp Met  
 300 305 310

tag aggggtgaggt ggagaaagaa tgggttggt tgtctgctgg agttggagac 2816

aggctatggt agaattgtca cggctgccag gatcttcacg tttagttttt tcttggaaaa 2876

aaaaaaaaatg atgtcttgaa actcagagcc accagtctgt tcaggactca tgggtctgtg 2936

tcctctggta gcctgtggat tgaatgtgct gactgtgctg tcttctcaca gtgccctcac 2996

ccctatcagt aacttgacag agacttgacc catgggtctc cagggtgact caccgaaaga 3056

cacaaagatg ctccaactt catttgctga agagaagact ttgaaaatct gagtttcttt 3116

tcttagtcat tgggaatttg gtgaactatc tactcaggac ctgggtgagg gccaacagta 3176

tatctgacat aggaatcctt cattcattct gactggtggt gtccagcttc tgatgaaaca 3236

ctcagtgtta ggaagtttga aacattccag ggctgcaggt tctgagtaag acacctatgc 3296

ttgctagaaa atcatttttt cacctaagcc agtatgtgta ttcttttgct.tatatattacc 3356

aatccatcct tatgtccaat tccttttatt aagtactttg aataagacat gtcctctggc 3416

tttatgtttc atgcaactct ttctttgcac atagatgtat cttatgtttt caagaatgag 3476

aatggctcat ttatttacta attccaccaa atctgtgata ggggatggg acacatatac 3536

taaattagggt gtgtcagact tgtgtatttg tcctaagaca gagaaggaaa tgataattat 3596

gatagattct gttctctgaa atttccatcc caaggcccag cataataaaa gaagagcaag 3656

accaagcaga taggaggcaa gaatattatg tttctctttt cctgtctcat gtgaacttac 3716

16U 200 PCT FINAL.ST25

ctactatata attctctatt aatcctgaca acacagctaa gcttttcaca caagccctgt 3776  
 ataaatacat tgttctgctg ttattctctg acccacttgt ttcctcagat attattgctt 3836  
 agaaattata tatctctttt gctatcactg tatctttctc tatttaccta tctatattat 3896  
 ttgaccttga aagataattt ccaagcctat ttcaggtggg gtgtagaagg ttggaagctg 3956  
 tccaggaggg aagagtatag caagaaccta gagttttact tccccctata tccacacctt 4016  
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 aaaattgcta catgctagat atatatattt ttggagtata tgtgatattc tgatatattc 4136  
 atataataga taatgatcaa atcaggataa ttggaatgc catgacctta aatgtttctt 4196  
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 accaatctgc tctctatttt catgagctgt acttagcctc cacatgagtg agaaatacaa 4436  
 taattgtctt tctgtacctg gcttgtttca cttaacttaa tgacctacag ttcatccac 4496  
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 tt 4558

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 <213> Homo sapiens

<400> 70

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Val Gly Ile Pro Gly Leu Glu His Leu His Ile Trp Ile Ser Ile Pro  
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Phe Cys Leu Ala Tyr Thr Leu Ala Leu Leu Gly Asn Cys Thr Leu Leu  
35 40 45

Leu Ile Ile Gln Ala Asp Ala Ala Leu His Glu Pro Met Tyr Leu Phe  
50 55 60

Leu Ala Met Leu Ala Ala Ile Asp Leu Val Leu Ser Ser Ser Ala Leu  
65 70 75 80

Pro Lys Met Leu Ala Ile Phe Trp Phe Arg Asp Arg Glu Ile Asn Phe  
85 90 95

Phe Ala Cys Leu Ala Gln Met Phe Phe Leu His Ser Phe Ser Ile Met  
100 105 110

Glu Ser Ala Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile  
115 120 125

Cys Lys Pro Leu His Tyr Thr Lys Val Leu Thr Gly Ser Leu Ile Thr  
130 135 140

Lys Ile Gly Met Ala Ala Val Ala Arg Ala Val Thr Leu Met Thr Pro  
145 150 155 160

16U 200 PCT FINAL.ST25  
 Leu Pro Phe Leu Leu Arg Cys Phe His Tyr Cys Arg Gly Pro Val Ile  
                   165                  170                  175

Ala His Cys Tyr Cys Glu His Met Ala Val Val Arg Leu Ala Cys Gly  
                   180                  185                  190

Asp Thr Ser Phe Asn Asn Ile Tyr Gly Ile Ala Val Ala Met Phe Ile  
                   195                  200                  205

Val Val Leu Asp Leu Leu Leu Val Ile Leu Ser Tyr Ile Phe Ile Leu  
                   210                  215                  220

Gln Ala Val Leu Leu Leu Ala Ser Gln Glu Ala His Tyr Lys Ala Phe  
                   225                  230                  235                  240

Gly Thr Cys Val Ser His Ile Gly Ala Ile Leu Ala Phe Tyr Thr Thr  
                   245                  250                  255

Val Val Ile Ser Ser Val Met His Arg Val Ala Arg His Ala Ala Pro  
                   260                  265                  270

His Val His Ile Leu Leu Ala Asn Phe Tyr Leu Leu Phe Pro Pro Met  
                   275                  280                  285

Val Asn Pro Ile Ile Tyr Gly Val Lys Thr Lys Gln Ile Arg Glu Ser  
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Ile Leu Gly Val Phe Pro Arg Lys Asp Met  
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<400> 71  
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<400> 72  
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<210> 73  
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 <213> Homo sapiens

<400> 73  
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 <213> Homo sapiens

<400> 74  
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<210> 75  
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 <212> DNA



16U 200 PCT FINAL.ST25

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

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&lt;210&gt; 76

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

cagcctccaa tatcacctta acacatcca 29

&lt;210&gt; 77

&lt;211&gt; 25

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

caccacaata aacatggcca cagcg 25

&lt;210&gt; 78

&lt;211&gt; 2520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (727)..(1722)

&lt;223&gt;

&lt;400&gt; 78

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gcccagttgg agccacccca agtgacacca gcaggcagat gaccagagag cctgagcctc 180

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cctccacaat cgtggccaag tggaaacctg tgtgtgactc tcattgctctg aagcccatgg 660

cccagtcctat ctacctggct gggattctgg tgggagctgc tgcgtgaggc cctgcctcag 720

acagtg atg gag tgg acg gcg gca cgg gcc cga ccc ttg gtg atg acc 768

Met Glu Trp Thr Ala Ala Arg Ala Arg Pro Leu Val Met Thr  
1 5 10

ttg aac tct ctg ggc ttc agc ttc ggc cat ggc ctg aca gct gca gtg 816

Leu Asn Ser Leu Gly Phe Ser Phe Gly His Gly Leu Thr Ala Ala Val  
15 20 25 30

gcc tac ggt gtg cgg gac tgg aca ctg ctg cag ctg gtg gtc tcg gtc 864

Ala Tyr Gly Val Arg Asp Trp Thr Leu Leu Gln Leu Val Val Ser Val  
35 40 45

ccc ttc ttc ctg tgc ttt ttg tac tcc tgg tgg ctg gca gag tcg gca 912

Pro Phe Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala  
50 55 60

cga tgg ctg ctg acc aca ggc agg ctg gat tgg ggc ctg cag gag ctg 960

Arg Trp Leu Leu Thr Thr Gly Arg Leu Asp Trp Gly Leu Gln Glu Leu  
65 70 75

16U 200 PCT FINAL.ST25

tgg agg gtg gct gcc atc aac gga aag ggg gca gtg cag gac acc ctg 1008  
 Trp Arg Val Ala Ala Ile Asn Gly Lys Gly Ala Val Gln Asp Thr Leu  
 80 85 90

acc cct gag gtc ttg ctt tca gcc atg cgg gag gag ctg agc atg ggc 1056  
 Thr Pro Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly  
 95 100 105 110

cag cct cct gcc agc ctg ggc acc ctg ctc cgc atg ccc gga ctg cgc 1104  
 Gln Pro Pro Ala Ser Leu Gly Thr Leu Arg Met Pro Gly Leu Arg  
 115 120 125

ttc cgg acc tgt atc tcc acg ttg tgc tgg ttc gcc ttt ggc ttc acc 1152  
 Phe Arg Thr Cys Ile Ser Thr Leu Cys Trp Phe Ala Phe Gly Phe Thr  
 130 135 140

ttc ttc ggc ctg gcc ctg gac ctg cag gcc ctg ggc agc aac atc ttc 1200  
 Phe Phe Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe  
 145 150 155

ctg ctc caa atg ttc att ggt gtc gtg gac atc cca gcc aag atg ggc 1248  
 Leu Leu Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly  
 160 165 170

gcc ctg ctg ctg ctg agc cac ctg ggc cgc cgc ccc acg ctg gcc gca 1296  
 Ala Leu Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala  
 175 180 185 190

tcc ctg ttg ctg gca ggg ctc tgc att ctg gcc aac acg ctg gtg ccc 1344  
 Ser Leu Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro  
 195 200 205

cac gaa atg ggg gct ctg cgc tca gcc ttg gcc gtg ctg ggg ctg ggc 1392  
 His Glu Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly  
 210 215 220

ggg gtg ggg gct gcc ttc acc tgc atc acc atc tac agc agc gag etc 1440  
 Gly Val Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu  
 225 230 235

ttc ccc act gtg ctc agg atg acg gca gtg ggc ttg ggc cag atg gca 1488  
 Phe Pro Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala  
 240 245 250

gcc cgt gga gga gcc atc ctg ggg cct ctg gtc cgg ctg ctg ggt gtc 1536  
 Ala Arg Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val  
 255 260 265 270

cat ggc ccc tgg ctg ccc ttg ctg gtg tat ggg acg gtg cca gtg ctg 1584  
 His Gly Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu  
 275 280 285

agt ggc ctg gcc gca ctg ctt ctg ccc gag acc cag agc ttg ccg ctg 1632  
 Ser Gly Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu  
 290 295 300

ccc gac acc atc caa gat gtg cag aac cag gca gta aag aag gca aca 1680  
 Pro Asp Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr  
 305 310 315

cat ggc acg ctg ggg aac tct gtc cta aaa tcc aca cag ttt 1722  
 His Gly Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe  
 320 325 330

tagcctctg gggaacctgc gatgggacgg tcagaggaag agacttcttc tgttctctg 1782

agaaggcagg aggaaagcaa agacctccat ttccagaggc ccagaggctg cctctgagg 1842

tccccactct cccccagggc tgcctctca ggtgagccct gcccctctca cagtccaagg 1902

ggcccccttc aatactgaag gggaaaagga cagtttgatt ggcaggaggt gaccagtg 1962

accatcaccc tgccctgcc tcgtggcttc ggagagcaga ggggtcaggc ccagggggaa 2022

gagctggcct tgccaacct ctgcttgact ccgcactgcc acttgctccc ccacacccgt 2082

ccacctgcc agagctcaga gctaaccacc atccatggc aagacctctc ctgctccac 2142

acaagcagta ggtctcagc tccacagctt taccagaag ccctgtaagc ctggccctg 2202

16U 200 PCT FINAL.ST25

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 ccccttccca cctcatccc tgaccgactc cacttaaccc ccaaaccag ccccccttcc 2322  
 aggggtccag ggcagcctg agatgcccg gaaactccta cccacagtta cagccacaag 2382  
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 <213> Homo sapiens

<400> 79

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Gly Val Arg Asp Trp Thr Leu Leu Gln Leu Val Val Ser Val Pro Phe  
 35 40 45

Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala Arg Trp  
 50 55 60

Leu Leu Thr Thr Gly Arg Leu Asp Trp Gly Leu Gln Glu Leu Trp Arg  
 65 70 75 80

Val Ala Ala Ile Asn Gly Lys Gly Ala Val Gln Asp Thr Leu Thr Pro  
 85 90 95

Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly Gln Pro  
 100 105 110

Pro Ala Ser Leu Gly Thr Leu Leu Arg Met Pro Gly Leu Arg Phe Arg  
 115 120 125

Thr Cys Ile Ser Thr Leu Cys Trp Phe Ala Phe Gly Phe Thr Phe Phe  
 130 135 140

Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe Leu Leu  
 145 150 155 160

Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly Ala Leu  
 165 170 175

Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala Ser Leu  
 180 185 190

Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro His Glu  
 195 200 205

Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly Gly Val  
 210 215 220

Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu Phe Pro  
 225 230 235 240

16U 200 PCT FINAL.ST25

Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala Ala Arg  
 245 250 255

Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val His Gly  
 260 265 270

Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu Ser Gly  
 275 280 285

Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu Pro Asp  
 290 295 300

Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr His Gly  
 305 310 315 320

Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe  
 325 330

<210> 80  
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 1 5 10

ggc tcc cag gat gcc ctg gcc ccc ttg cct cca cct gct ccc cag aat 99  
 Gly Ser Gln Asp Ala Leu Ala Pro Leu Pro Pro Pro Ala Pro Gln Asn  
 15 20 25 30

ccc tcc acc cac tct tgg gac cct ttg tgt gga tct ctg cct tgg ggc 147  
 Pro Ser Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly  
 35 40 45

ctc agc tgt ctt ctg gct ctg cag cat gtc ttg gtc atg gct tct ctg 195  
 Leu Ser Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu  
 50 55 60

ctc tgt gtc tcc cac ctg ctc ctg ctt tgc agt ctc tcc cca gga gga 243  
 Leu Cys Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly  
 65 70 75

ctc tct tac tcc cct tct cag ctc ctg gcc tcc agc ttc ttt tca tgt 291  
 Leu Ser Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys  
 80 85 90

ggc atg tct acc atc ctg caa act tgg atg ggc agc agg ctg cct ctt 339  
 Gly Met Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu  
 95 100 105 110

gtc cag gct cca tcc tta gag ttc ctt atc cct gct ctg gtg ctg acc 387  
 Val Gln Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr  
 115 120 125

agc cag aag cta ccc cgg gcc atc cag aca cct gga aac tcc tcc ctc 435  
 Ser Gln Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu  
 130 135 140

atg ctg cac ctt tgt agg gga cct agc tgc cat ggc ctg ggg cac tgg 483  
 Met Leu His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp  
 145 150 155

aac act tct ctc cag gag gtg tcc ggg gca gtg gta gta tct ggg ctg 531  
 Asn Thr Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu

160 165 160 200 PCT FINAL.ST25  
170

ctg cag ggc atg atg ggg ctg ctg ggg agt ccc ggc cac gtg ttc ccc 579  
Leu Gln Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro  
175 180 185 190

cac tgt ggg ccc ctg gtg ctg gct ccc agc ctg gtt gtg gca ggg ctc 627  
His Cys Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu  
195 200 205

tct gcc cac agg gag gta gcc cag ttc tgc ttc aca cac tgg ggg ttg 675  
Ser Ala His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu  
210 215 220

gcc ttg ctg tac gtg agt cct gag agg cgt ggg atg gtg ccc agt ggg 723  
Ala Leu Leu Tyr Val Ser Pro Glu Arg Arg Gly Met Val Pro Ser Gly  
225 230 235

ggt gta tgg ggg gac taggggaggg cagaactgct ggtcctatca gattcagcag 778  
Gly Val Trp Gly Asp  
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tgggtggtca cacctgtaat ctagcacgt ggggaggctg aggcaggcag atcacttagg 2038

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gagaatcgtg tgagcctggg aggcagaggt tgctgtgagc cgagaccgca ccaactgcact 2218

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20 25 30

Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly Leu Ser  
35 40 45

Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu Leu Cys  
50 55 60

Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly Leu Ser  
65 70 75 80

Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys Gly Met  
85 90 95

Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu Val Gln  
100 105 110

Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr Ser Gln  
115 120 125

Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu Met Leu  
130 135 140

His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp Asn Thr  
145 150 155 160

Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu Leu Gln  
165 170 175

Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro His Cys  
180 185 190

Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu Ser Ala  
195 200 205

His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu Ala Leu  
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Trp Gly Asp

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16U 200 PCT FINAL.ST25  
Met Asp Arg Gly Glu Lys  
1 5

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Ile Gln Leu Lys Arg Val Phe Gly Tyr Trp Trp Gly Thr Ser Phe Leu  
10 15 20

ctt att aat atc att ggt gca gga att ttt gtg tcc ccc aaa ggt gtg 212  
Leu Ile Asn Ile Ile Gly Ala Gly Ile Phe Val Ser Pro Lys Gly Val  
25 30 35

ttg gca tac tct tgc atg aac gtg gga gtc tcc ctg tgc gtt tgg gct 260  
Leu Ala Tyr Ser Cys Met Asn Val Gly Val Ser Leu Cys Val Trp Ala  
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Gly Cys Ala Ile Leu Ala Met Thr Ser Thr Leu Cys Ser Ala Glu Ile  
55 60 65 70

agt ata agc ttc cca tgc agt gga gct caa tac tat ttt ctc aag aga 356  
Ser Ile Ser Phe Pro Cys Ser Gly Ala Gln Tyr Tyr Phe Leu Lys Arg  
75 80 85

tac ttt ggc tcc acg gtt gct ttt ttg aat ctc tgg aca tcc ttg ttt 404  
Tyr Phe Gly Ser Thr Val Ala Phe Leu Asn Leu Trp Thr Ser Leu Phe  
90 95 100

ctg ggg tca ggg gta gtt gct ggc caa gct ctg ctc ctt gct gag tac 452  
Leu Gly Ser Gly Val Val Ala Gly Gln Ala Leu Leu Ala Glu Tyr  
105 110 115

agc atc cag cct ttt ttt ccc agc tgc tct gtc cca aag ctg cct aag 500  
Ser Ile Gln Pro Phe Phe Pro Ser Cys Ser Val Pro Lys Leu Pro Lys  
120 125 130

aaa tgt ctg gca ttg gcc atg ttg tgg att gta gga att ctg act tct 548  
Lys Cys Leu Ala Leu Ala Met Leu Trp Ile Val Gly Ile Leu Thr Ser  
135 140 145 150

cgt ggt gtg aaa gaa gtg act tgg ctt cag ata gct agc tca gtg ctg 596  
Arg Gly Val Lys Glu Val Thr Trp Leu Gln Ile Ala Ser Ser Val Leu  
155 160 165

aaa gtg tcc ata ctt agc ttc att tcc cta act gga gta gtg ttc ctg 644  
Lys Val Ser Ile Leu Ser Phe Ile Ser Leu Thr Gly Val Val Phe Leu  
170 175 180

ata aga ggg aaa aag gag aat gta gaa cga ttt cag aat gct ttt gat 692  
Ile Arg Gly Lys Lys Glu Asn Val Glu Arg Phe Gln Asn Ala Phe Asp  
185 190 195

gct gaa ctt cca gat atc tct cac ctt ata caa gcc atc ttc caa gga 740  
Ala Glu Leu Pro Asp Ile Ser His Leu Ile Gln Ala Ile Phe Gln Gly  
200 205 210

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Tyr Phe Ala Tyr Ser Gly Gly Ala Cys Phe Thr Leu Ile Ala Gly Glu  
215 220 225 230

ctg aag aag ccc aga aca aca att ccc aaa tgc ata ttt act gcg tta 836  
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235 240 245

cct ctg gtg act gta gtt tat tta ctg gtt aac att tcc tat ctg act 884  
Pro Leu Val Thr Val Val Tyr Leu Leu Val Asn Ile Ser Tyr Leu Thr  
250 255 260

gtt ctg aca ccc agg gaa att ctc tct tca gat gct gta gct atc aca 932  
Val Leu Thr Pro Arg Glu Ile Leu Ser Ser Asp Ala Val Ala Ile Thr  
265 270 275

tgg gct gat cga gct ttt ccc tca tta gca tgg att atg cct ttt gct 980  
Trp Ala Asp Arg Ala Phe Pro Ser Leu Ala Trp Ile Met Pro Phe Ala  
280 285 290

att tct acc tca tta ttt agc aac ctt ctg att tct ata ttt aaa tca 1028  
Ile Ser Thr Ser Leu Phe Ser Asn Leu Leu Ile Ser Ile Phe Lys Ser  
295 300 305 310

160 200 PCT FINAL.ST25

tcg aga cca ata tat ctt gca agc caa gag ggc cag ctg cct ttg cta 1076  
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 Phe Asn Thr Leu Asn Ser His Ser Ser Pro Phe Thr Ala Val Leu Leu  
 330 335 340

ctt gtc act ttg gga tcc ctt gca att atc tta aca agt cta att gat 1172  
 Leu Val Thr Leu Gly Ser Leu Ala Ile Ile Leu Thr Ser Leu Ile Asp  
 345 350 355

ttg ata aac tat att ttt ttc acg ggt tca tta tgg tct ata tta tta 1220  
 Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser Leu Trp Ser Ile Leu Leu  
 360 365 370

atg ata gga ata cta agg cgg aga tac cag gaa ccc aat cta tct ata 1268  
 Met Ile Gly Ile Leu Arg Arg Arg Tyr Gln Glu Pro Asn Leu Ser Ile  
 375 380 385 390

cct tat aag gtg ttt ttg tca ttt cca tta gca aca ata gtc atc gac 1316  
 Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu Ala Thr Ile Val Ile Asp  
 395 400 405

gtg ggc ttg gtt gtg ata cca ttg gta aag tct cca aat gtg cat tat 1364  
 Val Gly Leu Val Val Ile Pro Leu Val Lys Ser Pro Asn Val His Tyr  
 410 415 420

gtc tac gtg ctt ctg tta gtt ctc agc gga tta cta ttt tac ata cct 1412  
 Val Tyr Val Leu Leu Leu Val Leu Ser Gly Leu Leu Phe Tyr Ile Pro  
 425 430 435

tta ata cat ttt aaa ata aga ttg gct tgg ttt gag aag atg act tgc 1460  
 Leu Ile His Phe Lys Ile Arg Leu Ala Trp Phe Glu Lys Met Thr Cys  
 440 445 450

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 Tyr Leu Gln Leu Leu Phe Asn Ile Cys Leu Pro Asp Val Ser Glu Glu  
 455 460 465 470

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caaatcaagg ttaaacatat gatagaacat tcatggtgaa attcctatgg taaatatttt 1628

tttctcaaat gaaataagta atgtatacaa aagtgcctaa gacagtacct ggcttcagag 1688

tcactaagaa attgctaaaa gctctgcttc gcatggtaaa aaacttaagt cctggtttgc 1748

gtagcttgat agagtgatta tacaacttcc attctctcac ttttttttcc tgtatcccac 1808

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Val Ser Pro Lys Gly Val Leu Ala Tyr Ser Cys Met Asn Val Gly Val  
 35 40 45

Ser Leu Cys Val Trp Ala Gly Cys Ala Ile Leu Ala Met Thr Ser Thr  
 50 55 60

Leu Cys Ser Ala Glu Ile Ser Ile Ser Phe Pro Cys Ser Gly Ala Gln  
 65 70 75 80



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Tyr Tyr Phe Leu Lys Arg Tyr Phe Gly Ser Thr Val Ala Phe Leu Asn  
                   85                                  90                                  95

Leu Trp Thr Ser Leu Phe Leu Gly Ser Gly Val Val Ala Gly Gln Ala  
                   100                                  105                                  110

Leu Leu Leu Ala Glu Tyr Ser Ile Gln Pro Phe Phe Pro Ser Cys Ser  
                   115                                  120                                  125

Val Pro Lys Leu Pro Lys Lys Cys Leu Ala Leu Ala Met Leu Trp Ile  
                   130                                  135                                  140

Val Gly Ile Leu Thr Ser Arg Gly Val Lys Glu Val Thr Trp Leu Gln  
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Ile Ala Ser Ser Val Leu Lys Val Ser Ile Leu Ser Phe Ile Ser Leu  
                   165                                  170                                  175

Thr Gly Val Val Phe Leu Ile Arg Gly Lys Lys Glu Asn Val Glu Arg  
                   180                                  185                                  190

Phe Gln Asn Ala Phe Asp Ala Glu Leu Pro Asp Ile Ser His Leu Ile  
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Gln Ala Ile Phe Gln Gly Tyr Phe Ala Tyr Ser Gly Gly Ala Cys Phe  
                   210                                  215                                  220

Thr Leu Ile Ala Gly Glu Leu Lys Lys Pro Arg Thr Thr Ile Pro Lys  
                   225                                  230                                  235                                  240

Cys Ile Phe Thr Ala Leu Pro Leu Val Thr Val Val Tyr Leu Leu Val  
                   245                                  250                                  255

Asn Ile Ser Tyr Leu Thr Val Leu Thr Pro Arg Glu Ile Leu Ser Ser  
                   260                                  265                                  270

Asp Ala Val Ala Ile Thr Trp Ala Asp Arg Ala Phe Pro Ser Leu Ala  
                   275                                  280                                  285

Trp Ile Met Pro Phe Ala Ile Ser Thr Ser Leu Phe Ser Asn Leu Leu  
                   290                                  295                                  300

Ile Ser Ile Phe Lys Ser Ser Arg Pro Ile Tyr Leu Ala Ser Gln Glu  
                   305                                  310                                  315                                  320

Gly Gln Leu Pro Leu Leu Phe Asn Thr Leu Asn Ser His Ser Ser Pro  
                   325                                  330                                  335

Phe Thr Ala Val Leu Leu Leu Val Thr Leu Gly Ser Leu Ala Ile Ile  
                   340                                  345                                  350

Leu Thr Ser Leu Ile Asp Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser  
                   355                                  360                                  365

Leu Trp Ser Ile Leu Leu Met Ile Gly Ile Leu Arg Arg Arg Tyr Gln  
                   370                                  375                                  380

Glu Pro Asn Leu Ser Ile Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu  
                   385                                  390                                  395                                  400

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Ala Thr Ile Val Ile Asp Val Gly Leu Val Val Ile Pro Leu Val Lys  
 405 410 415

Ser Pro Asn Val His Tyr Val Tyr Val Leu Leu Leu Val Leu Ser Gly  
 420 425 430

Leu Leu Phe Tyr Ile Pro Leu Ile His Phe Lys Ile Arg Leu Ala Trp  
 435 440 445

Phe Glu Lys Met Thr Cys Tyr Leu Gln Leu Leu Phe Asn Ile Cys Leu  
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Pro Asp Val Ser Glu Glu  
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 Met Glu Val Lys Asn Phe Ala Val Trp Asp Tyr  
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 Val Val Phe Ala Ala Leu Phe Phe Ile Ser Ser Gly Ile Gly Val Phe  
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 Phe Ala Ile Lys Glu Arg Lys Lys Ala Thr Ser Arg Glu Phe Leu Val  
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 ggg gga agg caa atg agc ttt ggc cct gtc ggc ttg tct ctg aca gcc 495  
 Gly Gly Arg Gln Met Ser Phe Gly Pro Val Gly Leu Ser Leu Thr Ala  
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 Ser Phe Met Ser Ala Val Thr Val Leu Gly Thr Pro Ser Glu Val Tyr  
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 Arg Phe Gly Ala Ser Phe Leu Val Phe Phe Ile Ala Tyr Leu Phe Val  
 80 85 90  
 atc ctc tta aca tca gag ctc ttt ctc cct gtg ttc tac aga tct ggt 639  
 Ile Leu Leu Thr Ser Glu Leu Phe Leu Pro Val Phe Tyr Arg Ser Gly  
 95 100 105  
 atc acc agc act tat gag tac tta caa cta cga ttc aac aaa cca gtt 687  
 Ile Thr Ser Thr Tyr Glu Tyr Leu Gln Leu Arg Phe Asn Lys Pro Val  
 110 115 120  
 cgc tat gct gcc acg gtc atc tac att gta cag acg att ctc tac aca 735  
 Arg Tyr Ala Ala Thr Val Ile Tyr Ile Val Gln Thr Ile Leu Tyr Thr  
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160 200 PCT FINAL.ST25

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 140 145 150 155

ttt gat ctc tgg ggc tct gtg ttt gca aca gga att gtt tgc aca ttc 831  
 Phe Asp Leu Trp Gly Ser Val Phe Ala Thr Gly Ile Val Cys Thr Phe  
 160 165 170

tac tgt acc ctg gta tgt atc tagctgtgaa gaagtattta acactacctc 882  
 Tyr Cys Thr Leu Val Cys Ile  
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ttgtttaaca ttcttttcat taccaacctt taggagaatt taat 1046

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<400> 85

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Arg Lys Lys Ala Thr Ser Arg Glu Phe Leu Val Gly Gly Arg Gln Met  
 35 40 45

Ser Phe Gly Pro Val Gly Leu Ser Leu Thr Ala Ser Phe Met Ser Ala  
 50 55 60

Val Thr Val Leu Gly Thr Pro Ser Glu Val Tyr Arg Phe Gly Ala Ser  
 65 70 75 80

Phe Leu Val Phe Phe Ile Ala Tyr Leu Phe Val Ile Leu Leu Thr Ser  
 85 90 95

Glu Leu Phe Leu Pro Val Phe Tyr Arg Ser Gly Ile Thr Ser Thr Tyr  
 100 105 110

Glu Tyr Leu Gln Leu Arg Phe Asn Lys Pro Val Arg Tyr Ala Ala Thr  
 115 120 125

Val Ile Tyr Ile Val Gln Thr Ile Leu Tyr Thr Gly Val Val Val Tyr  
 130 135 140

Ala Pro Ala Leu Ala Leu Asn Gln Val Thr Gly Phe Asp Leu Trp Gly  
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Cys Ile

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Lys Arg Lys Thr Met Ala Lys Val Asn Arg Ala Arg Ser Thr Ser Pro
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cca gat gga ggc tgg ggc tgg atg att gtg gct ggc tgt ttc ctt gtt      555
Pro Asp Gly Gly Trp Gly Trp Met Ile Val Ala Gly Cys Phe Leu Val
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acc atc tgc aca cgg gca gtc aca aga tgt atc tca att ttt ttt gtg      603
Thr Ile Cys Thr Arg Ala Val Thr Arg Cys Ile Ser Ile Phe Phe Val
                        60          65          70

gag ttc cag aca tac ttc act cag gat tac gca caa acg gca tgg atc      651
Glu Phe Gln Thr Tyr Phe Thr Gln Asp Tyr Ala Gln Thr Ala Trp Ile
                        75          80          85          90

cat tcc att gta gat tgt gtg acc atg ctc tgt gct cca ctt ggg agt      699
His Ser Ile Val Asp Cys Val Thr Met Leu Cys Ala Pro Leu Gly Ser
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gtt gtc agt aac cat tta tcc tgt caa gtg gga atc atg ctg ggt ggc      747
Val Val Ser Asn His Leu Ser Cys Gln Val Gly Ile Met Leu Gly Gly
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Leu Leu Ala Ser Thr Gly Leu Ile Leu Ser Ser Phe Ala Thr Ser Leu
                        125          130          135

aag cat ctc tac ctc act ctg gga gtt ctt aca ggt ctt gga ttt gca      843
Lys His Leu Tyr Leu Thr Leu Gly Val Leu Thr Gly Leu Gly Phe Ala
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ctt tgt tac tct cca gct att gcc atg gtt ggc aag tac ttc agc aga      891
Leu Cys Tyr Ser Pro Ala Ile Ala Met Val Gly Lys Tyr Phe Ser Arg
-155          160          165          170

cgg aaa gcc ctt gct tat ggt atc gcc atg tca gga agt ggc att ggc      939
Arg Lys Ala Leu Ala Tyr Gly Ile Ala Met Ser Gly Ser Gly Ile Gly
                        175          180          185

acc ttc atc ctg gct cct gtg gtt cag ctc ctt att gaa cag ttt tcc      987
Thr Phe Ile Leu Ala Pro Val Val Gln Leu Leu Ile Glu Gln Phe Ser
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Trp Arg Gly Ala Leu Leu Ile Leu Gly Gly Phe Val Leu Asn Leu Cys
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gta tgt ggt gcc ttg atg agg cca att act ctt aaa gag gac cac aca      1083
Val Cys Gly Ala Leu Met Arg Pro Ile Thr Leu Lys Glu Asp His Thr
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16U 200 PCT FINAL.ST25

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 255 260 265

ctc tgt tgc tgt ttg cag caa gag tac agt ttt tta ctc atg tca gac 1227  
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 Phe Val Val Leu Ala Val Ser Val Leu Phe Met Ala Tyr Gly Cys Ser  
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 Pro Leu Phe Val Tyr Leu Val Pro Tyr Ala Leu Ser Val Gly Val Ser  
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 His Gln Gln Ala Ala Phe Leu Met Ser Ile Leu Gly Val Ile Asp Ile  
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att ggc aat atc aca ttt gga tgg ctg acc gac aga agg tgt ctg aag 1419  
 Ile Gly Asn Ile Thr Phe Gly Trp Leu Thr Asp Arg Arg Cys Leu Lys  
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aat tac cag tat gtt tgc tac ctc ttt gcc gtg gga atg gat ggg ctc 1467  
 Asn Tyr Gln Tyr Val Cys Tyr Leu Phe Ala Val Gly Met Asp Gly Leu  
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tgc tat ctc tgc ctc cca atg ctt caa agt ctc cct ctg ctc gtg cct 1515  
 Cys Tyr Leu Cys Leu Pro Met Leu Gln Ser Leu Pro Leu Leu Val Pro  
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ttc tct tgt acc ttt ggc tac ttt gat ggt gcc tat gtg act ttg atc 1563  
 Phe Ser Cys Thr Phe Gly Tyr Phe Asp Gly Ala Tyr Val Thr Leu Ile  
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cca gta gtg acc aca gag ata gtg ggg acc acc tct ttg tca tca gcg 1611  
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ctt ggt gtg gta tac ttc ctt cac gca gtg cca tac ttg gtg agc cca 1659  
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ccc atc gca gga cgg ctg gta gat acc acc ggc agc tac act gca gca 1707  
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ttc ctc ctc tgt gga ttt tca atg ata ttt agt tct gtg ttg ctt ggc 1755  
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ttt gct aga ctt ata aag aga atg aga aaa acc cag ttg cag ttc att 1803  
 Phe Ala Arg Leu Ile Lys Arg Met Arg Lys Thr Gln Leu Gln Phe Ile  
 460 465 470

gcc aaa gaa tct gat cct aag ctg cag cta tgg-acc aat gga tca gtg 1851  
 Ala Lys Glu Ser Asp Pro Lys Leu Gln Leu Trp Thr Asn Gly Ser Val  
 475 480 485 490

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 Ala Tyr Ser Val Ala Arg Glu Leu Asp Gln Lys His Gly Glu Pro Val  
 495 500 505

gct aca gca gtg cct ggc tac agc ctc aca tgaccaaagg ccttgagccc 1949  
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16U 200 PCT FINAL.ST25

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16U 200 PCT FINAL.ST25

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Trp Met Ile Val Ala Gly Cys Phe Leu Val Thr Ile Cys Thr Arg Ala  
 50 55 60

Val Thr Arg Cys Ile Ser Ile Phe Phe Val Glu Phe Gln Thr Tyr Phe  
 65 70 75 80

Thr Gln Asp Tyr Ala Gln Thr Ala Trp Ile His Ser Ile Val Asp Cys  
 85 90 95

Val Thr Met Leu Cys Ala Pro Leu Gly Ser Val Val Ser Asn His Leu  
 100 105 110

Ser Cys Gln Val Gly Ile Met Leu Gly Gly Leu Leu Ala Ser Thr Gly  
 115 120 125

Leu Ile Leu Ser Ser Phe Ala Thr Ser Leu Lys His Leu Tyr Leu Thr  
 130 135 140

Leu Gly Val Leu Thr Gly Leu Gly Phe Ala Leu Cys Tyr Ser Pro Ala  
 145 150 155 160

Ile Ala Met Val Gly Lys Tyr Phe Ser Arg Arg Lys Ala Leu Ala Tyr  
 165 170 175

Gly Ile Ala Met Ser Gly Ser Gly Ile Gly Thr Phe Ile Leu Ala Pro  
 180 185 190

Val Val Gln Leu Leu Ile Glu Gln Phe Ser Trp Arg Gly Ala Leu Leu  
 195 200 205

Ile Leu Gly Gly Phe Val Leu Asn Leu Cys Val Cys Gly Ala Leu Met  
 210 215 220

Arg Pro Ile Thr Leu Lys Glu Asp His Thr Thr Pro Glu Gln Asn His  
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Val Cys Arg Thr Gln Lys Glu Asp Ile Lys Arg Val Ser Pro Tyr Ser  
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160 200 PCT FINAL.ST25  
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 275 280 285

Ser Val Leu Phe Met Ala Tyr Gly Cys Ser Pro Leu Phe Val Tyr Leu  
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Val Pro Tyr Ala Leu Ser Val Gly Val Ser His Gln Gln Ala Ala Phe  
 305 310 315 320

Leu Met Ser Ile Leu Gly Val Ile Asp Ile Ile Gly Asn Ile Thr Phe  
 325 330 335

Gly Trp Leu Thr Asp Arg Arg Cys Leu Lys Asn Tyr Gln Tyr Val Cys  
 340 345 350

Tyr Leu Phe Ala Val Gly Met Asp Gly Leu Cys Tyr Leu Cys Leu Pro  
 355 360 365

Met Leu Gln Ser Leu Pro Leu Leu Val Pro Phe Ser Cys Thr Phe Gly  
 370 375 380

Tyr Phe Asp Gly Ala Tyr Val Thr Leu Ile Pro Val Val Thr Thr Glu  
 385 390 395 400

Ile Val Gly Thr Thr Ser Leu Ser Ser Ala Leu Gly Val Val Tyr Phe  
 405 410 415

Leu His Ala Val Pro Tyr Leu Val Ser Pro Pro Ile Ala Gly Arg Leu  
 420 425 430

Val Asp Thr Thr Gly Ser Tyr Thr Ala Ala Phe Leu Leu Cys Gly Phe  
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Ser Met Ile Phe Ser Ser Val Leu Leu Gly Phe Ala Arg Leu Ile Lys  
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Arg Met Arg Lys Thr Gln Leu Gln Phe Ile Ala Lys Glu Ser Asp Pro  
 465 470 475 480

Lys Leu Gln Leu Trp Thr Asn Gly Ser Val Ala Tyr Ser Val Ala Arg  
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Tyr Ser Leu Thr  
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<400> 88



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tgc cct gcc ctc agc agg ctg gtt ccc aga ggc ttt ggg act gag atg 155  
Cys Pro Ala Leu Ser Arg Leu Val Pro Arg Gly Phe Gly Thr Glu Met  
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tgg act ctc ttt gcc ctt tct gga ccc ctg ttc ctg ttc cag gtg ctg 203  
Trp Thr Leu Phe Ala Leu Ser Gly Pro Leu Phe Leu Phe Gln Val Leu  
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act ttt atg atc tac atc gtg agc act gtg ttc tgc ggg cac ctg ggc 251  
Thr Phe Met Ile Tyr Ile Val Ser Thr Val Phe Cys Gly His Leu Gly  
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aag gtg gag ctg gca tcg gtg acc ctc gcg gtg gcc ttt gtc aat gtc 299  
Lys Val Glu Leu Ala Ser Val Thr Leu Ala Val Ala Phe Val Asn Val  
65 70 75

tgc gga gtt tct gta gga gtt ggt ttg tct tcg gca tgt gac acc ttg 347  
Cys Gly Val Ser Val Gly Val Gly Leu Ser Ser Ala Cys Asp Thr Leu  
80 85 90 95

atg tct cag agc ttc ggc agc ccc aac aag aag cac gtg ggc gtg atc 395  
Met Ser Gln Ser Phe Gly Ser Pro Asn Lys Lys His Val Gly Val Ile  
100 105 110

ctg cag cgg ggc gcg ctg gtc ctg ctc ctc tgc tgc ctc cct tgc tgg 443  
Leu Gln Arg Gly Ala Leu Val Leu Leu Cys Cys Leu Pro Cys Trp  
115 120 125

gcg ctc ttc ctc aac acc cag cac atc ctg ctg ctc ttc cgg cag gac 491  
Ala Leu Phe Leu Asn Thr Gln His Ile Leu Leu Leu Phe Arg Gln Asp  
130 135 140

ccg gac gtg tcc agg ttg acc cag gac tat gta atg att ttc att cca 539  
Pro Asp Val Ser Arg Leu Thr Gln Asp Tyr Val Met Ile Phe Ile Pro  
145 150 155

gga ctt ccg gtg att ttt ctt tac aat ctg ctg gca aaa tat ttg caa 587  
Gly Leu Pro Val Ile Phe Leu Tyr Asn Leu Leu Ala Lys Tyr Leu Gln  
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aat cag aag atc acc tgg ccc caa gtc ctc agt ggt gtg gtg ggc aac 635  
Asn Gln Lys Ile Thr Trp Pro Gln Val Leu Ser Gly Val Val Gly Asn  
180 185 190

tgt gtc aac ggt gtg gcc aac tat gcc ctg gtt tct gtg ctg aac ctg 683  
Cys Val Asn Gly Val Ala Asn Tyr Ala Leu Val Ser Val Leu Asn Leu  
195 200 205

ggg gtc agg ggc tcc gcc tat gcc aac atc atc tcc cag ttt gca cag 731  
Gly Val Arg Gly Ser Ala Tyr Ala Asn Ile Ile Ser Gln Phe Ala Gln  
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acc gtc ttc ctc ctt ctc tac att gtg ctg aag aag ctg cac ctg gag 779  
Thr Val Phe Leu Leu Leu Tyr Ile Val Leu Lys Lys Leu His Leu Glu  
225 230 235

acg tgg gca ggt tgg tcc agc cag tgc ctg cag gac tgg ggc ccc ttc 827  
Thr Trp Ala Gly Trp Ser Ser Gln Cys Leu Gln Asp Trp Gly Pro Phe  
240 245 250 255

ttc tcc ctg gct gtc ccc agc atg ctc atg atc tgt gtt gag tgg tgg 875  
Phe Ser Leu Ala Val Pro Ser Met Leu Met Ile Cys Val Glu Trp Trp  
260 265 270

gcc tat gag atc ggg agc ttc ctc atg ggg ctg ctc agt gtg gtg gat 923  
Ala Tyr Glu Ile Gly Ser Phe Leu Met Gly Leu Leu Ser Val Val Asp  
275 280 285

ctc tct gcc cag gct gtc atc tac gag gtg gcc act gtg acc tac atg 971  
Leu Ser Ala Gln Ala Val Ile Tyr Glu Val Ala Thr Val Thr Tyr Met  
290 295 300

att ccc ttg ggg ctc agc atc ggg gtc tgt gtc cga gtg ggg atg gct 1019

160 200 PCT FINAL.ST25

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ctg ggg gct gcg gat act gtg cag gcc aag cgc tgc gcc gtc tgc ggc		1067
Leu Gly Ala Ala Asp Thr Val Gln Ala Lys Arg Ser Ala Val Ser Gly		
320	325	330
gtg ctc agc ata gtt ggc att tcc ctg gtc ctg ggc acc ctg ata agc		1115
Val Leu Ser Ile Val Gly Ile Ser Leu Val Leu Gly Thr Leu Ile Ser		
	340	345
atc ctg aaa aat cag ctg ggg cat att ttt acc aat gat gaa gat gtc		1163
Ile Leu Lys Asn Gln Leu Gly His Ile Phe Thr Asn Asp Glu Asp Val		
	355	360
att gcc ctg gtg agc cag gtc ttg ccg gtt tat agt gtc ttt cac gtg		1211
Ile Ala Leu Val Ser Gln Val Leu Pro Val Tyr Ser Val Phe His Val		
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Phe Glu Ala Ile Cys Cys Val Tyr Gly Gly Val Leu Arg Gly Thr Gly		
	385	390
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	400	405
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Gly Leu Pro Leu Gly Ile Leu Leu Thr Phe Val Val Arg Met Arg Ile		
	420	425
atg ggc ctc tgg ctg ggc atg ctg gcc tgt gtc ttc ctg gca act gct		1403
Met Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala		
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gcc ttt gtt gct tat act gcc cgg ctg gac tgg aag ctt gct gca gag		1451
Ala Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu		
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Glu Ala Lys Lys His Ser Gly Arg Gln Gln Gln Gln Arg Ala Glu Ser		
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Thr Ala Thr Arg Pro Gly Pro Glu Lys Ala Val Leu Ser Ser Val Ala		
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Thr Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu		
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tgc cac gtg gac ttc ttc agg act cca gag gag gcc cac gcc ctt tca		1643
Cys His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser		
	515	520
gct cct acc agc aga cta tca gtg aaa cag ctg gtc atc cgc cgt ggg		1691
Ala Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly		
	530	535
gct gct ctg ggg gcg gcg tca gcc aca ctg atg gtg ggg ctc acg gtc		1739
Ala Ala Leu Gly Ala Ala Ser Ala Thr Leu Met Val Gly Leu Thr Val		
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Arg Ile Leu Ala Thr Arg His		
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Phe Met Ile Tyr Ile Val Ser Thr Val Phe Cys Gly His Leu Gly Lys  
 50 55 60

Val Glu Leu Ala Ser Val Thr Leu Ala Val Ala Phe Val Asn Val Cys  
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Gly Val Ser Val Gly Val Gly Leu Ser Ser Ala Cys Asp Thr Leu Met  
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Ser Gln Ser Phe Gly Ser Pro Asn Lys Lys His Val Gly Val Ile Leu  
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Gln Arg Gly Ala Leu Val Leu Leu Leu Cys Cys Leu Pro Cys Trp Ala  
 115 120 125

Leu Phe Leu Asn Thr Gln His Ile Leu Leu Leu Phe Arg Gln Asp Pro  
 130 135 140

Asp Val Ser Arg Leu Thr Gln Asp Tyr Val Met Ile Phe Ile Pro Gly  
 145 150 155 160

Leu Pro Val Ile Phe Leu Tyr Asn Leu Leu Ala Lys Tyr Leu Gln Asn  
 165 170 175

Gln Lys Ile Thr Trp Pro Gln Val Leu Ser Gly Val Val Gly Asn Cys  
 180 185 190

Val Asn Gly Val Ala Asn Tyr Ala Leu Val Ser Val Leu Asn Leu Gly  
 195 200 205

Val Arg Gly Ser Ala Tyr Ala Asn Ile Ile Ser Gln Phe Ala Gln Thr  
 210 215 220

Val Phe Leu Leu Leu Tyr Ile Val Leu Lys Lys Leu His Leu Glu Thr  
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Trp Ala Gly Trp Ser Ser Gln Cys Leu Gln Asp Trp Gly Pro Phe Phe  
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Ser Leu Ala Val Pro Ser Met Leu Met Ile Cys Val Glu Trp Trp Ala  
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Tyr Glu Ile Gly Ser Phe Leu Met Gly Leu Leu Ser Val Val Asp Leu  
 275 280 285

16U 200 PCT FINAL.ST25

Ser Ala Gln Ala Val Ile Tyr Glu Val Ala Thr Val Thr Tyr Met Ile  
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Pro Leu Gly Leu Ser Ile Gly Val Cys Val Arg Val Gly Met Ala Leu  
 305 310 315 320

Gly Ala Ala Asp Thr Val Gln Ala Lys Arg Ser Ala Val Ser Gly Val  
 325 330 335

Leu Ser Ile Val Gly Ile Ser Leu Val Leu Gly Thr Leu Ile Ser Ile  
 340 345 350

Leu Lys Asn Gln Leu Gly His Ile Phe Thr Asn Asp Glu Asp Val Ile  
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Ala Leu Val Ser Gln Val Leu Pro Val Tyr Ser Val Phe His Val Phe  
 370 375 380

Glu Ala Ile Cys Cys Val Tyr Gly Gly Val Leu Arg Gly Thr Gly Lys  
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 405 410 415

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Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala Ala  
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Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu Glu  
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Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu Cys  
 500 505 510

His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser Ala  
 515 520 525

Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly Ala  
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&lt;210&gt; 90

&lt;211&gt; 3067

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

16U 200 PCT FINAL.ST25

&lt;221&gt; CDS

&lt;222&gt; (36).. (2984)

&lt;223&gt;

&lt;400&gt; 90

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Gly Gln Glu Gly Phe Glu Ala Ser Ser Ala Pro Arg Asn Ile Pro Ser
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ggg gag ctg gac agc aac cct gac cct ggc acc ggc ccc agc cct gat      149
Gly Glu Leu Asp Ser Asn Pro Asp Pro Gly Thr Gly Pro Ser Pro Asp
                25                30                35

ggc ccc tca gac aca gag agc aag gaa ctg gga gta ccc aaa gac cct      197
Gly Pro Ser Asp Thr Glu Ser Lys Glu Leu Gly Val Pro Lys Asp Pro
                40                45                50

ctg ctc ttc att cag ctg aat gag ctg ctg ggc tgg ccc cag gcg ctg      245
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Glu Trp Arg Glu Thr Gly Ser Ser Ser Ala Ser Leu Leu Leu Asp Met
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Gly Glu Met Pro Ser Ile Thr Leu Ser Thr His Leu His His Arg Trp
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Val Leu Phe Glu Glu Lys Leu Glu Val Ala Ala Gly Arg Trp Ser Ala
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ccc cac gtg ccc acc ctg gca ctg ccc agc ctc cag aag ctc cgc agc      437
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Gly Ser Thr His Pro Arg Lys Ala Ser Asp Asn Glu Glu Ala Pro Leu



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160 200 PCT FINAL.ST25

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 485 490 495  
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 Arg Glu His Pro Gly Leu Gly Gln Leu Glu Pro Pro His Cys His Tyr  
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16U 200 PCT FINAL.ST25

<400> 142  
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<400> 145  
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<400> 146  
gtgatgtctc gagaatgagt gcggttg 27

<210> 147  
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<210> 148  
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<213> Homo sapiens

<400> 148  
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<210> 149  
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<400> 149  
gcagatgacc cgacctgact gttcttc 27

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<400> 150  
tggctgtgca gctagctcag gtaccag 27

<210> 151  
<211> 50

160 200 PCT FINAL.ST25

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 151

gccagagagt ttaaataaag ccctactttg gggcaggagc gggaggaaac 50

&lt;210&gt; 152

&lt;211&gt; 945

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)...(945)

&lt;223&gt;

&lt;400&gt; 152

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Met Gly Val Lys Asn His Ser Thr Val Thr Glu Phe Leu Leu Ser Gly

1 5 10 15

tta act gaa caa gca gag ctt cag ctg ccc ctc ttc tgc ctc ttc tta 96  
Leu Thr Glu Gln Ala Glu Leu Gln Leu Pro Leu Phe Cys Leu Phe Leu

20 25 30

gga att tac aca gtt act gtg gtg gga aac ctc agc atg atc tca att 144  
Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile

35 40 45

att agg ctg aat cgt caa ctt cat acc ccc atg tac tat ttc ctg agt 192  
Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser

50 55 60

agt ttg tct ttt tta gat ttc tgc tat tct tct gtc att acc cct aaa 240  
Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys

65 70 75 80

atg cta tca ggg ttt tta tgc aga gat aga tcc atc tcc tat tct gga 288  
Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly

85 90 95

tgc atg att cag ctg ttt ttt ttc tgt gtt tgt gtt att tct gaa tgc 336  
Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys

100 105 110

tac atg ctg gca gcc atg gcc tgc gat cgc tac gtg gcc atc tgc agc 384  
Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser

115 120 125

cca ctg ctc tac agg gtc atc atg tcc cct agg gtc tgt tct ctg ctg 432  
Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu

130 135 140

gtg gct gct gtc ttc tca gta ggt ttc act gat gct gtg atc cat gga 480  
Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly

145 150 155 160

ggg tgt ata ctc agg ttg tct ttc tgt gga tca aac atc att aaa cat 528  
Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His

165 170 175

tat ttc tgt gac att gtc cct ctt att aaa ctc tcc tgc tcc agc act 576  
Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr

180 185 190

tat att gat gag ctt ttg att ttt gtc att ggt gga ttt aac atg gtg 624  
Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val

195 200 205

gcc aca agc cta aca atc att att tca tat gct ttt atc ctc acc agc 672  
Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser

210 215 220

atc ctg cgc atc cac tct aaa aag ggc agg tgc aaa gcg ttt agc acc 720  
Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr

225 230 235 240

tgt agc tcc cac ctg aca gct gtt ctt atg ttt tat ggg tct ctg atg 768

16U 200 PCT FINAL.ST25  
 Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met  
                   245                  250                  255  
 tcc atg tat ctc aaa cct gct tct agc agt tca ctc acc cag gag aaa 816  
 Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Leu Thr Gln Glu Lys  
                   260                  265                  270  
 gta tcc tca gta ttt tat acc act gtg att ctc atg ttg aat ccc ttg 864  
 Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu  
                   275                  280                  285  
 ata tat agt ctg agg aac aat gaa gta aga aat gct ctg atg aaa ctt 912  
 Ile Tyr Ser Leu Arg Asn Asn Glu Val Arg Asn Ala Leu Met Lys Leu  
                   290                  295                  300  
 tta aga aga aaa ata tct tta tct cca gga taa 945  
 Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly  
                   305                  310

<210> 153  
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 <212> PRT  
 <213> Homo sapiens

<400> 153

Met Gly Val Lys Asn His Ser Thr Val Thr Glu Phe Leu Leu Ser Gly  
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Leu Thr Glu Gln Ala Glu Leu Gln Leu Pro Leu Phe Cys Leu Phe Leu  
                   20                  25                  30

Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile  
                   35                  40                  45

Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser  
                   50                  55                  60

Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys  
                   65                  70                  75                  80

Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly  
                   85                  90                  95

Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys  
                   100                  105                  110

Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser  
                   115                  120                  125

Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu  
                   130                  135                  140

Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly  
                   145                  150                  155                  160

Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His  
                   165                  170                  175

Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr  
                   180                  185                  190

Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val  
                   195                  200                  205



16U 200 PCT FINAL.ST25  
 Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser  
 210 215 220

Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr  
 225 230 235 240

Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met  
 245 250 255

Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Ser Leu Thr Gln Glu Lys  
 260 265 270

Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu  
 275 280 285

Ile Tyr Ser Leu Arg Asn Asn Glu Val Arg Asn Ala Leu Met Lys Leu  
 290 295 300

Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly  
 305 310

<210> 154  
 <211> 34  
 <212> DNA  
 <213> Homo sapiens

<400> 154  
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<210> 155  
 <211> 36  
 <212> DNA  
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<400> 155  
 tcatcagagc atttcttact tcattgttcc tcagac 36

<210> 156  
 <211> 50  
 <212> DNA  
 <213> Homo sapiens

<400> 156  
 caggagaatt aaatataaga gtggtcagtg tgtttgtaac actcaggaca 50

<210> 157  
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 <212> DNA  
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<400> 157  
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<210> 158  
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 <212> DNA  
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<400> 158  
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<210> 159  
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<400> 159

## 16U 200 PCT FINAL.ST25

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 <213> Homo sapiens

<400> 160  
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<210> 161  
 <211> 50  
 <212> DNA  
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<400> 161  
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<210> 162  
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 <212> DNA  
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<220>  
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<400> 162  
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 Met Asn Pro Ala Asn His Ser Gln Val Ala Gly Phe Val Leu Leu Gly  
 1 5 10 15

ctc tct cag gtt tgg gag ctt cgg ttt gtt ttc ttc act gtt ttc tct 96  
 Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Thr Val Phe Ser  
 20 25 30

gct gtg tat ttt atg act gta gtg gga aac ctt ctt att gtg gtc ata 144  
 Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile  
 35 40 45

gtg acc tcc gac cca cac ctg cac aca acc atg tat ttt ctc ttg ggc 192  
 Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly  
 50 55 60

aat ctt tct ttc ctg gac ttt tgc tac tct tcc atc aca gca cct agg 240  
 Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg  
 65 70 75 80

atg ctg gtt gac ttg ctc tca ggc aac cct acc att tcc ttt ggt gga 288  
 Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly  
 85 90 95

tgc ctg act caa ctc ttc ttc ttc cac ttc att gga ggc atc aag atc 336  
 Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile  
 100 105 110

ttc ctg ctg act gtc atg gcg tat gac cgc tac att gcc att tcc cag 384  
 Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln  
 115 120 125

ccc ctg cac tac acg ctc att atg aat cag act gtc tgt gca ctc ctt 432  
 Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu  
 130 135 140

atg gca gcc tcc tgg gtg ggg ggc ttc atc cac tcc ata gta cag att 480  
 Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile  
 145 150 155 160

gca ttg act atc cag ctg cca ttc tgt ggg cct gac aag ctg gac aac 528  
 Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn  
 165 170 175

ttt tat tgt gat gtg cct cag ctg atc aaa ttg gcc tgc aca gat acc 576  
 Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr  
 180 185 190

## 16U 200 PCT FINAL.ST25

ttt gtc tta gag ctt tta atg gtg tct aac aat ggc ctg gtg acc ctg 624  
 Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu  
 195 200 205

atg tgt ttt ctg gtg ctt ctg gga tgc tac aca gca ctg cta gtc atg 672  
 Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met  
 210 215 220

ctc cga agc cac tca cgg gag ggc cgc agc aag gcc ctg tct acc tgt 720  
 Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys  
 225 230 235 240

gcc tct cac att gct gtg gtg acc tta atc ttt gtg cct tgc atc tac 768  
 Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr  
 245 250 255

gtc tat aca agg cct ttt cgg aca ttc ccc atg gac aag gcc gtc tct 816  
 Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser  
 260 265 270

gtg cta tac aca att gtc acc ccc atg ctg aat cct gcc atc tat acc 864  
 Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr  
 275 280 285

ctg aga aac aag gaa gtg atc atg gcc atg aag aag ctg tgg agg agg 912  
 Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg  
 290 295 300

aaa aag gac cct att ggt ccc ctg gag cac aga ccc tta cat tag 957  
 Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His  
 305 310 315

<210> 163  
 <211> 318  
 <212> PRT  
 <213> Homo sapiens

<400> 163

Met Asn Pro Ala Asn His Ser Gln Val Ala Gly Phe Val Leu Leu Gly  
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Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Phe Thr Val Phe Ser  
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Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile  
 35 40 45

Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly  
 50 55 60

Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg  
 65 70 75 80

Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly  
 85 90 95

Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile  
 100 105 110

Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln  
 115 120 125

Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu  
 130 135 140

Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile  
 145 150 155 160

16U 200 PCT FINAL.ST25

Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn  
 165 170 175

Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr  
 180 185 190

Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu  
 195 200 205

Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met  
 210 215 220

Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys  
 225 230 235 240

Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr  
 245 250 255

Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser  
 260 265 270

Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr  
 275 280 285

Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg  
 290 295 300

Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His  
 305 310 315

<210> 164  
 <211> 26  
 <212> DNA  
 <213> Homo sapiens

<400> 164  
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<210> 165  
 <211> 29  
 <212> DNA  
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<400> 165  
 ctaatgtaag ggtctgtgct ccaggggac 29

<210> 166  
 <211> 50  
 <212> DNA  
 <213> Homo sapiens

<400> 166  
 cactaccctt ttaaagtgca gggggcagtg atttcttttc ttttctttt 50

<210> 167  
 <211> 972  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(972)  
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160 200 PCT FINAL.ST25

<400> 167  
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 Met Asn Pro Glu Asn Trp Thr Gln Val Thr Ser Phe Val Leu Leu Gly  
 1 5 10 15

ttc ccc agt agc cac ctc ata cag ttc ctg gtg ttc ctg ggg tta atg 96  
 Phe Pro Ser Ser His Leu Ile Gln Phe Leu Val Phe Leu Gly Leu Met  
 20 25 30

gtg acc tac att gta aca gcc aca ggc aag ctg cta att att gtg ctc 144  
 Val Thr Tyr Ile Val Thr Ala Thr Gly Lys Leu Leu Ile Ile Val Leu  
 35 40 45

agc tgg ata gac caa cgc ctg cac ata cag atg tac ttc ttc ctg cgg 192  
 Ser Trp Ile Asp Gln Arg Leu His Ile Gln Met Tyr Phe Phe Leu Arg  
 50 55 60

aat ttc tcc ttc ctg gag ctg ttg ctg gta act gtt gtg gtt ccc aag 240  
 Asn Phe Ser Phe Leu Glu Leu Leu Leu Val Thr Val Val Val Pro Lys  
 65 70 75 80

atg ctt gtc gtc atc ctc acg ggg gat cac acc atc tca ttt gtc agc 288  
 Met Leu Val Val Ile Leu Thr Gly Asp His Thr Ile Ser Phe Val Ser  
 85 90 95

tgc atc atc cag tcc tac ctc tac ttc ttt cta ggc acc act gac ttc 336  
 Cys Ile Ile Gln Ser Tyr Leu Tyr Phe Phe Leu Gly Thr Thr Asp Phe  
 100 105 110

ttc ctc ttg gcc gtc atg tct ctg gat cgt tac ctg gca atc tgc cga 384  
 Phe Leu Leu Ala Val Met Ser Leu Asp Arg Tyr Leu Ala Ile Cys Arg  
 115 120 125

cca ctc cgc tat gag acc ctg atg aat ggc cat gtc tgt tcc caa cta 432  
 Pro Leu Arg Tyr Glu Thr Leu Met Asn Gly His Val Cys Ser Gln Leu  
 130 135 140

gtg ctg gcc tcc tgg cta gct gga ttc ctc tgg gtc ctt tgc ccc act 480  
 Val Leu Ala Ser Trp Leu Ala Gly Phe Leu Trp Val Leu Cys Pro Thr  
 145 150 155 160

gtc ctc atg gcc agc ctg cct ttc tgt ggc ccc aat ggt att gac cac 528  
 Val Leu Met Ala Ser Leu Pro Phe Cys Gly Pro Asn Gly Ile Asp His  
 165 170 175

ttc ttt cgt gac agt tgg ccc ttg ctc agg ctt tct tgt ggg gac acc 576  
 Phe Phe Arg Asp Ser Trp Pro Leu Leu Arg Leu Ser Cys Gly Asp Thr  
 180 185 190

cac ctg ctg aaa ctg gtg gct ttc atg ctc tct acg ttg gtg tta ctg 624  
 His Leu Leu Lys Leu Val Ala Phe Met Leu Ser Thr Leu Val Leu Leu  
 195 200 205

ggc tca ctg gct ctg acc tca gtt tcc tat gcc tgc att ctt gcc act 672  
 Gly Ser Leu Ala Leu Thr Ser Val Ser Tyr Ala Cys Ile Leu Ala Thr  
 210 215 220

gtt ctc agg gcc cct aca gct gct gag cga agg aaa gcg ttt tcc act 720  
 Val Leu Arg Ala Pro Thr Ala Ala Glu Arg Arg Lys Ala Phe Ser Thr  
 225 230 235 240

tgc gcc tgc cat ctt aca gtg gtg gtc atc atc tat ggc agt tcc atc 768  
 Cys Ala Ser His Leu Thr Val Val Val Ile Ile Tyr Gly Ser Ser Ile  
 245 250 255

ttt ctc tac att cgt atg tca gag gct cag tcc aaa ctg ctc aac aaa 816  
 Phe Leu Tyr Ile Arg Met Ser Glu Ala Gln Ser Lys Leu Leu Asn Lys  
 260 265 270

ggc gcc tcc gtc ctg agc tgc atc atc aca ccc ctc ttg aac cca ttc 864  
 Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe  
 275 280 285

atc ttc act ctc cgc aat gac aag gtg cag caa gca ctg aga gaa gcc 912  
 Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala  
 290 295 300

ttg ggg tgg ccc agg ctc act gct gtg atg aaa ctg agg gtc aca agt 960  
 Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser

972

16U 200 PCT FINAL.ST25  
270

260

265

Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe  
275 280 285

Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala  
290 295 300

Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser  
305 310 315 320

Gln Arg Lys

<210> 169  
<211> 25  
<212> DNA  
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<400> 169  
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<210> 170  
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<212> DNA  
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<400> 170  
ctgagaacag tggcaagaat gcaggcatag 30

<210> 171  
<211> 450  
<212> DNA  
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<220>  
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<222> (1)..(450)  
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<400> 171  
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1 5 10 15

ttc ctg gtg gtt tat gtg ctt act gtg ctg ggg aac ctc ctc atc ctg 96  
Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu  
20 25 30

ctg gtg atc agg gtg tac tct cac ctc cac acc ccc aag tac tac ttc 144  
Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe  
35 40 45

etc acc aat ctg tcc ttc att gac ttg tgg ttc ttc act gtc atg gtg 192  
Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val  
50 55 60

ccc aaa atg ccg agg acc ttg ttg tcc ctg tgt ggc aag gct gtg tcc 240  
Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser  
65 70 75 80

ttc cac agt tgt atg acc caa ctc tat ttc ttc tac ttc ctg ggg agc 288  
Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser  
85 90 95

acc gag tgt ttg ctc tac acg gtc atg tcc tat gat cgc tat aga gga 336  
Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly  
100 105 110

aat act cag cac ttc cca ggt agt gaa aac act ccc cac gaa gtg agc 384  
Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser  
115 120 125

## 16U 200 PCT FINAL.ST25

caa atg cta gtg gcc cgg ggg gca cac ggg ctc cca ctc atc atc ctg 432  
 Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu  
 130 135 140

gca gat ctg agt ggg taa 450  
 Ala Asp Leu Ser Gly  
 145

<210> 172  
 <211> 149  
 <212> PRT  
 <213> Homo sapiens

<400> 172

Met Asp Leu Pro His Val Pro Ala Leu Asp Ala Pro Leu Phe Gly Val  
 1 5 10 15

Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Ile Leu  
 20 25 30

Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe  
 35 40 45

Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val  
 50 55 60

Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser  
 65 70 75 80

Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser  
 85 90 95

Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly  
 100 105 110

Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser  
 115 120 125

Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu  
 130 135 140

Ala Asp Leu Ser Gly  
 145

<210> 173  
 <211> 23  
 <212> DNA  
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<400> 173  
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<210> 174  
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 <213> Homo sapiens

<400> 174  
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<210> 175  
 <211> 936  
 <212> DNA  
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&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(936)

&lt;223&gt;

&lt;400&gt; 175

atg tcc aac gcc agc ctc gtg aca gca ttc atc ctc aca ggc ctt ccc	48
Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro	
1 5 10 15	
cat gcc cca ggg ctg gac gcc ctc ctc ttt gga atc ttc ctg gtg gtt	96
His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val	
20 25 30	
tac gtg ctc act gtg ctg ggg aac ctc ctc atc ctg ctg gtg atc agg	144
Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg	
35 40 45	
gtg gat tct cac ctc cac acc ccc atg tac tac ttc ctc acc aac ctg	192
Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu	
50 55 60	
tcc ttc att gac atg tgg ttc tcc act gtc acg gtg ccc aaa atg ctg	240
Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu	
65 70 75 80	
atg acc ttg gtg tcc cca agc ggc agg gct atc tcc ttc cac agc tgc	288
Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys	
85 90 95	
gtg gct cag ctc tat ttt ttc cac ttc ctg ggg agc acc gag tgt ttc	336
Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe	
100 105 110	
ctc tac aca gtc atg tcc tat gat cgc tac ttg gcc atc agt tac ccg	384
Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro	
115 120 125	
ctc agg tac acc agc atg atg agt ggg agc agg tgt gcc ctc ctg gcc	432
Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala	
130 135 140	
acc ggc act tgg ctc agt ggc tct ctg cac tct gct gtc cag acc ata	480
Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile	
145 150 155 160	
ttg act ttc cat ttg ccc tac tgt gga ccc aac cag atc cag cac tac	528
Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr	
165 170 175	
ttc tgt gac gca ccg ccc atc ctg aaa ctg gcc tgt gca gac acc tca	576
Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser	
180 185 190	
gcc aac gtg atg gtc atc ttt gtg gac att ggg ata gtg gcc tca ggc	624
Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly	
195 200 205	
tgc ttt gtc ctg ata gtg ctg tcc tat gtg tcc atc gtc tgt tcc atc	672
Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile	
210 215 220	
ctg cgg atc cgc acc tca gat ggg agg cgc aga gcc ttt cag acc tgt	720
Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Arg Ala Phe Gln Thr Cys	
225 230 235 240	
gcc tcc cac tgt att gtg gtc ctt tgc ttc ttt gtt ccc tgt gtt gtc	768
Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val	
245 250 255	
att tat ctg agg cca ggc tcc atg gat gcc atg gat gga gtt gtg gcc	816
Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala	
260 265 270	
att ttc tac act gtg ctg acg ccc ctt ctc aac cct gtt gtg tac acc	864
Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr	
275 280 285	

16U 200 PCT FINAL.ST25  
 ctg aga aac aag gag gtg aag aaa gct gtg ttg aaa ctt aga gac aaa 912  
 Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys  
 290 295 300

gta gca cat cct cag agg aaa taa 936  
 Val Ala His Pro Gln Arg Lys  
 305 310

<210> 176  
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<400> 176

Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro  
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His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val  
 20 25 30

Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg  
 35 40 45

Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu  
 50 55 60

Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu  
 65 70 75 80

Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys  
 85 90 95

Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe  
 100 105 110

Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro  
 115 120 125

Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala  
 130 135 140

Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile  
 145 150 155 160

Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr  
 165 170 175

Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser  
 180 185 190

Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly  
 195 200 205

Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile  
 210 215 220

Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Arg Ala Phe Gln Thr Cys  
 225 230 235 240

Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val  
 245 250 255

## 16U 200 PCT FINAL.ST25

Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala  
 260 265 270

Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr  
 275 280 285

Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys  
 290 295 300

Val Ala His Pro Gln Arg Lys  
 305 310

<210> 177  
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<400> 177  
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<210> 178  
 <211> 33  
 <212> DNA  
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<400> 178  
 ttatttcctc tgaggatgtg ctactttgtc tct 33

<210> 179  
 <211> 50  
 <212> DNA  
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<400> 179  
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<210> 180  
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 <212> DNA  
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<400> 180  
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<210> 181  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)..(921)  
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<400> 181  
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 Met Val Thr Glu Phe Leu Leu Leu Gly Phe Ser His Leu Ala Asp Leu  
 1 5 10 15

cag ggc ttg ctc ttc tct gtc ttt ctc act atc tac ctg ctg acc gtg 96  
 Gln Gly Leu Leu Phe Ser Val Phe Leu Thr Ile Tyr Leu Leu Thr Val  
 20 25 30

gca ggc aat ttc ctc att gtg gtg ctg gtc tcc act gat gct gcc ctc 144  
 Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu  
 35 40 45

cag tcc cct atg tac ttc ttc ctg cgc acc ctc tgg gcc ttg gag att 192  
 Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile  
 50 55 60

## 16U 200 PCT FINAL.ST25

ggc tat acg tct gtc acg gtc ccc ctg cta ctt cac cac ctc ctt act 240  
 Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr  
 65 70 75 80

ggc cgg cgc cac atc tct cgc tct gga tgt gct ctc cag atg ttc ttc 288  
 Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe  
 85 90 95

ttc ctc ttc ttt ggc gcc acg gag tgc tgc ctc ctg gca gcc atg gcc 336  
 Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala  
 100 105 110

tat gac cgc tat gca gcc atc tgt gaa ccc ctc cgc tac cca ctg ctg 384  
 Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu  
 115 120 125

ctg agc cac cgg gtg tgt cta cag cta gct ggg tcg gcg tgg gcc tgt 432  
 Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys  
 130 135 140

ggg gtg ctg gtg ggg ctg ggc cac acc cct ttc atc ttc tct ttg ccc 480  
 Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro  
 145 150 155 160

ttc tgc ggc ccc aat acc atc ccg cag ttc ttc tgt gag atc cag cct 528  
 Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro  
 165 170 175

gtc ctg cag ctg gta tgt gga gac acc tcg ctt aat gaa ctg cag att 576  
 Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile  
 180 185 190

atc ctg gca aca gcc ctc ctc atc ctc tgc ccc ttt ggc ctc atc ctg 624  
 Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu  
 195 200 205

ggc tcc tac ggg cgt atc ctc gtt acc atc ttc cgg atc cca tct gtt 672  
 Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Phe Arg Ile Pro Ser Val  
 210 215 220

gcg ggc cgc cgc aag gcc ttc tcc acc tgc tcc tcc cac ctg atc gtg 720  
 Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val  
 225 230 235 240

gtc tcc ctc ttc tat ggc acc gca ctc ttt atc tat att cgc cct aag 768  
 Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys  
 245 250 255

gcc agc tac gat ccg gcc act gac cct ctg gtg tcc ctc ttc tat gct 816  
 Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala  
 260 265 270

gtg gtc acc ccc atc ctc aac ccc atc atc tac agc ctg cgg aac aca 864  
 Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr  
 275 280 285

gag gtc aaa gct gcc cta aag aga acc atc cag aaa acg gtg cct atg 912  
 Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met  
 290 295 300

gag att tga 921  
 Glu Ile  
 305

<210> 182  
 <211> 306  
 <212> PRT  
 <213> Homo sapiens

<400> 182

Met Val Thr Glu Phe Leu Leu Leu Gly Phe Ser His Leu Ala Asp Leu  
 1 5 10 15

Gln Gly Leu Leu Phe Ser Val Phe Leu Thr Ile Tyr Leu Leu Thr Val  
 20 25 30

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Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu  
 35 40 45  
 Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile  
 50 55 60  
 Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr  
 65 70 75 80  
 Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe  
 85 90 95  
 Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala  
 100 105 110  
 Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu  
 115 120 125  
 Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys  
 130 135 140  
 Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro  
 145 150 155 160  
 Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro  
 165 170 175  
 Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile  
 180 185 190  
 Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu  
 195 200 205  
 Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Phe Arg Ile Pro Ser Val  
 210 215 220  
 Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val  
 225 230 235 240  
 Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys  
 245 250 255  
 Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala  
 260 265 270  
 Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr  
 275 280 285  
 Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met  
 290 295 300  
 Glu Ile  
 305  
 <210> 183  
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16U 200 PCT FINAL.ST25

<400> 183  
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<210> 184  
<211> 23  
<212> DNA  
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<400> 184  
ggcgccaaag aagaggaaga aga 23

<210> 185  
<211> 897  
<212> DNA  
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<400> 185  
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Met Gly Arg Gly Asn Ser Thr Glu Val Thr Glu Phe His Leu Leu Gly  
1 5 10 15  
ttt ggt gtc caa cac gaa ttt cag cat gtc ctt ttc att gta ctt ctt 96  
Phe Gly Val Gln His Glu Phe Gln His Val Leu Phe Ile Val Leu Leu  
20 25 30  
ctt atc tat gtg acc tcc ctg ata gga aat att gga atg atc tta ctc 144  
Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu  
35 40 45  
atc aag acc gat tcc aga ctt caa aca ccc atg tac ttt ttt cca caa 192  
Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln  
50 55 60  
cat ttg gct ttt gtt gat atc tgt tat act tct gct atc act ccc aag 240  
His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys  
65 70 75 80  
atg ctc caa agc ttc aca gaa gaa aat aat ttg ata aca ttt cgg ggc 288  
Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly  
85 90 95  
tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt 336  
Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
100 105 110  
tac ctc cta gct att atg gca atg gat tgt tat gtt gcc atc tgt aag 384  
Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys  
115 120 125  
ccc ctt cgc tat ccc atg atc atg tcc caa aca gtc tac atc caa ctc 432  
Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu  
130 135 140  
gta gct ggc tca tat att ata ggc tca ata aat gcc tct gta cat aca 480  
Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr  
145 150 155 160  
ggc ttt aca ttt tca ctg tcc ttc tgc aag tct aat aaa atc aat cac 528  
Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His  
165 170 175  
ttt ttc tgt gat ggt ctc cca att ctt gcc ctt tca tgc tcc aac att 576  
Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile  
180 185 190  
gac atc aac atc att cta gat gtt gtc ttt gtg gga ttt gac ttg atg 624  
Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met  
195 200 205  
ttc act gag ttg gtc atc atc ttt tcc tac atc tac att atg gtc acc 672  
Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr  
210 215 220

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atc ctg aag atg tct tct act gct ggg agg aaa aaa tcc ttc tcc aca 720  
 ile leu lys met ser ser thr ala gly arg lys lys ser phe ser thr  
 225 230 235 240

tgt gcc tcc cac ctg aca gca gta acc att ttc tat ggg aca ctc tct 768  
 cys ala ser his leu thr ala val thr ile phe tyr gly thr leu ser  
 245 250 255

tac atg tac tta cag cct cag tct aat aat tct cag gag aat atg aaa 816  
 tyr met tyr leu gln pro gln ser asn asn ser gln glu asn met lys  
 260 265 270

gta gcc tct ata ttt tat ggc act gtt att ccc atg ttg aat cct tta 864  
 val ala ser ile phe tyr gly thr val ile pro met leu asn pro leu  
 275 280 285

atc tat agc ttg aga aat aag gaa gga aaa taa 897  
 ile tyr ser leu arg asn lys glu gly lys  
 290 295

<210> 186  
 <211> 298  
 <212> PRT  
 <213> Homo sapiens  
 <400> 186

Met Gly Arg Gly Asn Ser Thr Glu Val Thr Glu Phe His Leu Leu Gly  
 1 5 10 15

Phe Gly Val Gln His Glu Phe Gln His Val Leu Phe Ile Val Leu Leu  
 20 25 30

Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu  
 35 40 45

Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln  
 50 55 60

His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys  
 65 70 75 80

Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly  
 85 90 95

Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
 100 105 110

Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys  
 115 120 125

Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu  
 130 135 140

Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr  
 145 150 155 160

Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His  
 165 170 175

Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile  
 180 185 190

Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met  
 195 200 205

## 16U 200 PCT FINAL.ST25

Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr  
210 215 220

Ile Leu Lys Met Ser Ser Thr Ala Gly Arg Lys Lys Ser Phe Ser Thr  
225 230 235 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser  
245 250 255

Tyr Met Tyr Leu Gln Pro Gln Ser Asn Asn Ser Gln Glu Asn Met Lys  
260 265 270

Val Ala Ser Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu  
275 280 285

Ile Tyr Ser Leu Arg Asn Lys Glu Gly Lys  
290 295

<210> 187  
<211> 930  
<212> DNA  
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<220>  
<221> CDS  
<222> (1)..(930)  
<223>

<400> 187

atg aca cta gga aac agc act gaa gtc act gaa ttc tat ctt ctg gga 48  
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1 5 10 15

ttt ggt gcc cag cat gag ttt tgg tgt atc ctc ttc att gta ttc ctt 96  
Phe Gly Ala Gln His Glu Phe Trp Cys Ile Leu Phe Ile Val Phe Leu  
20 25 30

ctc atc tat gtg acc tcc ata atg ggt aat agt gga ata atc tta ctc 144  
Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu  
35 40 45

atc aac aca gat tcc aga ttt caa aca ctc acg tac ttt ttt cta caa 192  
Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln  
50 55 60

cat ttg gct ttt gtt gat atc tgt tac act tct gct atc act ccc aag 240  
His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys  
65 70 75 80

atg ctc caa agc ttc aca gaa gaa aag aat ttg atg tta ttt cag ggc 288  
Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly  
85 90 95

tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt 336  
Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
100 105 110

tat ctc ctg gct atg atg gca gtg gat cct tat gtt gcc atc tgt aag 384  
Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys  
115 120 125

ccc ctt cac tat act gta atc atg tcc cga aca gtc tgc atc cgt ttg 432  
Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu  
130 135 140

gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta caa aca 480  
Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr  
145 150 155 160

ggc ttt aca tgt tca ctg tcc ttc tgc aag tcc aat agc atc aat cac 528  
Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His



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165 170 175

ttt ttc tgt gat gtt ccc cct att ctt gct ctt tca tgc tcc aat gtt 576  
Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val  
180 185 190

gac atc aac atc atg cta ctt gtt gtc ttt gtg gga tct aac ttg ata 624  
Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile  
195 200 205

ttc act ggg ttg gtc gtc atc ttt tcc tac atc tac atc atg gcc acc 672  
Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr  
210 215 220

atc ctg aaa atg tct tct agt gca gga agg aaa aaa tcc ttc tca aca 720  
Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr  
225 230 235 240

tgt gct tcc cac ctg acc gca gtc acc att ttc tat ggg aca ctc tct 768  
Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser  
245 250 255

tac atg tat ttg cag tct cat tct aat aat tcc cag gaa aat atg aaa 816  
Tyr Met Tyr Leu Gln Ser His Ser Asn Asn Ser Gln Glu Asn Met Lys  
260 265 270

gtg gcc ttt ata ttt tat ggc aca gtt att ccc atg tta aat cct tta 864  
Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu  
275 280 285

atc tat agc ttg aga aat aag gaa gta aaa gaa gct tta aaa gtg ata 912  
Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile  
290 295 300

ggg aaa aag tta ttt taa 930  
Gly Lys Lys Leu Phe  
305

<210> 188  
<211> 309  
<212> PRT  
<213> Homo sapiens

<400> 188

Met Thr Leu Gly Asn Ser Thr Glu Val Thr Glu Phe Tyr Leu Leu Gly  
1 5 10 15

Phe Gly Ala Gln His Glu Phe Trp Cys Ile Leu Phe Ile Val Phe Leu  
20 25 30

Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu  
35 40 45

Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln  
50 55 60

His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys  
65 70 75 80

Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly  
85 90 95

Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
100 105 110

Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys  
115 120 125

Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu

16U 200 PCT FINAL.ST25  
140

130

135

Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr  
145 150 155 160

Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His  
165 170 175

Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val  
180 185 190

Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile  
195 200 205

Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr  
210 215 220

Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr  
225 230 235 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser  
245 250 255

Tyr Met Tyr Leu Gln Ser His Ser Asn Asn Ser Gln Glu Asn Met Lys  
260 265 270

Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu  
275 280 285

Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile  
290 295 300

Gly Lys Lys Leu Phe  
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1 5 10 15

tgc atg ata caa tta ttg gtt tat gca aca ttt gca acc agt gac tgt 96  
Cys Met Ile Gln Leu Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
20 25 30

tat ctc ctg gct atg ata gca gtg gac cat tat gtt gca atc tgt aag 144  
Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys  
35 40 45

ccc ctt cac tat acc gta atc acg tcc caa aca gtc tgc atc cat ttg 192  
Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu  
50 55 60

gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta cat aca 240  
Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr  
65 70 75 80

ggg ttt gca ttt tca ctg tct ttc tgc aag tcc aat aac atc aac cac 288

160 200 PCT FINAL.ST25

Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His  
                   85                  90                  95  
 ttt ttc tgt gat ggt ccc cca att ctt gcc ctt tca tgc tcc aat att      336  
 Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile  
                   100                  105                  110  
 gac atc aac atc atg cta ctt gtt gtc ttt gtg gga ttt aac ttg atg      384  
 Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met  
                   115                  120                  125  
 ttc act ggg ttg gag aat atg aaa gtg gcc tct ata ttt tat ggc act      432  
 Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr  
                   130                  135                  140  
 gtt att ccc atg ttg aat cct tta atc tat agc ttg aga aat aag gaa      480  
 Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu  
                   145                  150                  155                  160  
 gta aaa gaa gct tta aaa ttg ata ggg aaa aag ttc ttt taa      522  
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 Cys Met Ile Gln Leu Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys  
           20                  25                  30  
 Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys  
           35                  40                  45  
 Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu  
           50                  55                  60  
 Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr  
   65                  70                  75                  80  
 Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His  
                   85                  90                  95  
 Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile  
                   100                  105                  110  
 Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met  
   -          115                  120                  125  
 Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr  
           130                  135                  140  
 Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu  
   145                  150                  155                  160  
 Val Lys Glu Ala Leu Lys Leu Ile Gly Lys Lys Phe Phe  
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&lt;223&gt;

&lt;400&gt; 191

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 Met Ser Gln Arg  
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ctc tgc att aag cta tta gtt agt tca tat gtc atg ggt ttc cta aat 102  
 Leu Cys Ile Lys Leu Leu Val Ser Ser Tyr Val Met Gly Phe Leu Asn  
 5 10 15 20

gcc tct ata aac ata agt ttc act ttc tca ttg aac ttc tgc aaa tcc 150  
 Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn Phe Cys Lys Ser  
 25 30 35

aaa aca att aat cac ttt ttc tgt gat gaa cct cca att att gcc cta 198  
 Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro Ile Ile Ala Leu  
 40 45 50

cca tgc tcc aat att gac ctc aac atc atg tta tta aca gta ttt gtg 246  
 Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu Thr Val Phe Val  
 55 60 65

gga tta aat ttg atg tgc act gtg atg gtg gtc atc att tcc tgc ata 294  
 Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile Ile Ser Cys Ile  
 70 75 80

tat gtc ctg gtt gcc atc ctg agg ata tct tct gct gca ggg aag aaa 342  
 Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala Ala Gly Lys Lys  
 85 90 95 100

aaa gtc tct cta cat gtg cct ccc acc tga cagcagtcac cattttctat 392  
 Lys Val Ser Leu His Val Pro Pro Thr  
 105

ggggttctct cttacatgta tctatgccat cgtattaatg agtctcaaaa acaagaaaaa 452

gtggcctctg tgttttatgg cattattatt cccatgtaa acccctt 499

&lt;210&gt; 192

&lt;211&gt; 109

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 192

Met Ser Gln Arg Leu Cys Ile Lys Leu Leu Val Ser Ser Tyr Val Met  
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Gly Phe Leu Asn Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn  
 20 25 30

Phe Cys Lys Ser Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro  
 35 40 45

Ile Ile Ala Leu Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu  
 50 55 60

Thr Val Phe Val Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile  
 65 70 75 80

Ile Ser Cys Ile Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala  
 85 90 95

Ala Gly Lys Lys Lys Val Ser Leu His Val Pro Pro Thr  
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16U 200 PCT FINAL.ST25

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cgg gcc aca ttc cca gag tta tgt gcc agt ctt gtt gag gct tca cac 96  
 Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His  
 20 25 30

ctt ggc ggc ttt gta aac tca acc atc atc acc agt gag aca cct acc 144  
 Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr  
 35 40 45

ttg agc ttc tgt ggc agc aat atc att gat gat ttc ttc tgt gat ctg 192  
 Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu  
 50 55 60

ccc cca ctt gta aag ttg gtg tgt gat gtg aag gag cgc tac cag gct 240  
 Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala  
 65 70 75 80

gtg ctg cat ttt atg ctt gcc tcc aat cat cac tcc cac tgc act tat 288  
 Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr  
 85 90 95

tct tgc gtc cat ctc ttc atc att gca gcc atc tcg aag atc cgt tcc 336  
 Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser  
 100 105 110

att aag ggc cgc ctc cag gtc ttc tcc act tgt ggg tct ccc ctg acg 384  
 Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr  
 115 120 125

gct ctc acc ttg tac tat ggt gca atc ttc ttt att tac tcc caa cca 432  
 Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro  
 130 135 140

aga act agc tat gcc tta aaa atg gat aaa ttg ggg tca gtg ttc tat 480  
 Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr  
 145 150 155 160

act gtg gtg att cca atg cta aac ccc ttg atc tat agc tta aga aat 528  
 Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn  
 165 170 175

aag gat gtc aaa gat gcc ttg aag aaa atg tta gat aga ctt cag ttt 576  
 Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe  
 180 185 190

ctt aaa gaa aaa tat tgt aga tat ggg ctg gcc tgt agt gag cgc tac 624  
 Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr  
 195 200 205

ctc ctg gct gcc atg ggt tat gac tgc tat gag gca atc tcc aag ccc 672  
 Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro  
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ctg ctt taa 681  
 Leu Leu  
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<210> 194  
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&lt;400&gt; 194

16U 200 PCT FINAL.ST25

Met Ala Tyr Asp Arg Tyr Met Ala Ile Ser Lys Pro Leu Leu Tyr Ser  
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Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His  
 20 25 30

Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr  
 35 40 45

Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu  
 50 55 60

Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala  
 65 70 75 80

Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr  
 85 90 95

Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser  
 100 105 110

Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr  
 115 120 125

Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro  
 130 135 140

Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr  
 145 150 155 160

Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn  
 165 170 175

Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe  
 180 185 190

Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr  
 195 200 205

Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro  
 210 215 220

Leu Leu  
 225

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 Ser Asp Ala Gly Thr Ser Cys Pro Val Leu Cys Thr Cys Arg Asn Gln  
 20 25 30

48

96

16U 200 PCT FINAL.ST25

gtg gtg gat tgt agc agc cag cgg cta ttc tcc gtg ccc cca gac ctg 144  
Val Val Asp Cys Ser Ser Gln Arg Leu Phe Ser Val Pro Pro Asp Leu  
35 40 45

cca atg gac acc cga aac ctc agc ctg gcc cac aac cgc atc aca gca 192  
Pro Met Asp Thr Arg Asn Leu Ser Leu Ala His Asn Arg Ile Thr Ala  
50 55 60

gtg ccg cct ggc tac ctc aca tgc tac atg gag ctc cag gtg ctg gat 240  
Val Pro Pro Gly Tyr Leu Thr Cys Tyr Met Glu Leu Gln Val Leu Asp  
65 70 75 80

ttg cac aac aac tcc tta atg gag ctg ccc cgg ggc ctc ttc ctc cat 288  
Leu His Asn Asn Ser Leu Met Glu Leu Pro Arg Gly Leu Phe Leu His  
85 90 95

gcc aag cgc ttg gca cac ttg gac ctg agc tac aac aat ttc agc cat 336  
Ala Lys Arg Leu Ala His Leu Asp Leu Ser Tyr Asn Asn Phe Ser His  
100 105 110

gtg cca gcc gac atg ttc cag gag gcc cat ggg cta gtc cac atc gac 384  
Val Pro Ala Asp Met Phe Gln Glu Ala His Gly Leu Val His Ile Asp  
115 120 125

ctg agc cac aac ccc tgg ctg cgg agg gtg cat ccc cag gcc ttt cag 432  
Leu Ser His Asn Pro Trp Leu Arg Arg Val His Pro Gln Ala Phe Gln  
130 135 140

ggc ctc atg cag ctc cga gac ctg gac ctc agt tat ggg ggc ctg gcc 480  
Gly Leu Met Gln Leu Arg Asp Leu Asp Leu Ser Tyr Gly Gly Leu Ala  
145 150 155 160

ttc ctc agc ctg gag gct ctt gag ggc cta ccg ggg ctg gtg acc ctg 528  
Phe Leu Ser Leu Glu Ala Leu Glu Gly Leu Pro Gly Leu Val Thr Leu  
165 170 175

cag atc ggt ggc aat ccc tgg gtg tgt ggc tgc acc atg gaa ccc ctg 576  
Gln Ile Gly Gly Asn Pro Trp Val Cys Gly Cys Thr Met Glu Pro Leu  
180 185 190

ctg aag tgg ctg cga aac cgg atc cag cgc tgt aca gca gag tca ggt 624  
Leu Lys Trp Leu Arg Asn Arg Ile Gln Arg Cys Thr Ala Glu Ser Gly  
195 200 205

tct ggc ctg ccg gaa gag tca gaa cct gag tcc tgg act ggc caa agg 672  
Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg  
210 215 220

gct gca gta gag ttc cag gac ctc atg cag ctc caa gac ctg gat ctc 720  
Ala Ala Val Glu Phe Gln Asp Leu Met Gln Leu Gln Asp Leu Asp Leu  
225 230 235 240

agc tac gag aac ctg gct ttc ctc aaa ctc aag gcc ctg agc agt gta 768  
Ser Tyr Glu Asn Leu Ala Phe Leu Lys Leu Lys Ala Leu Ser Ser Val  
245 250 255

aac ttt ggg cac agg caa gcg gtt gtg ggt gga ctt tcc aat ccc ctc 816  
Asn Phe Gly His Arg Gln Ala Val Val Gly Gly Leu Ser Asn Pro Leu  
260 265 270

tcc ttc cct ggg tac ctc acc ctc cct ggc ttc tgt gtt aca gat tct 864  
Ser Phe Pro Gly Tyr Leu Thr Leu Pro Gly Phe Cys Val Thr Asp Ser  
275 280 285

cag ctg gct gag tgc cgg ggc cct cct gaa gtc gag ggc gcc ccg ctc 912  
Gln Leu Ala Glu Cys Arg Gly Pro Pro Glu Val Glu Gly Ala Pro Leu  
290 295 300

ttc tca ctc act gag gag agc ttc aag gcc tgc cac ctg acc ctg acc 960  
Phe Ser Leu Thr Glu Glu Ser Phe Lys Ala Cys His Leu Thr Leu Thr  
305 310 315 320

ctg gat gat tac cta ttc att gcg ttc gtg ggc ttc gtg gtc tcc att 1008  
Leu Asp Asp Tyr Leu Phe Ile Ala Phe Val Gly Phe Val Val Ser Ile  
325 330 335

gct tct gtg gcc acc aac ttc ctc ctg ggc atc act gcc aac tgc tgc 1056  
Ala Ser Val Ala Thr Asn Phe Leu Leu Gly Ile Thr Ala Asn Cys Cys  
340 345 350

160 200 PCT FINAL.ST25

cac cgc tgg agc aag gcc agt gaa gag gaa gag atc tga  
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 355 360

1095

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Ser Asp Ala Gly Thr Ser Cys Pro Val Leu Cys Thr Cys Arg Asn Gln  
 20 25 30

Val Val Asp Cys Ser Ser Gln Arg Leu Phe Ser Val Pro Pro Asp Leu  
 35 40 45

Pro Met Asp Thr Arg Asn Leu Ser Leu Ala His Asn Arg Ile Thr Ala  
 50 55 60

Val Pro Pro Gly Tyr Leu Thr Cys Tyr Met Glu Leu Gln Val Leu Asp  
 65 70 75 80

Leu His Asn Asn Ser Leu Met Glu Leu Pro Arg Gly Leu Phe Leu His  
 85 90 95

Ala Lys Arg Leu Ala His Leu Asp Leu Ser Tyr Asn Asn Phe Ser His  
 100 105 110

Val Pro Ala Asp Met Phe Gln Glu Ala His Gly Leu Val His Ile Asp  
 115 120 125

Leu Ser His Asn Pro Trp Leu Arg Arg Val His Pro Gln Ala Phe Gln  
 130 135 140

Gly Leu Met Gln Leu Arg Asp Leu Asp Leu Ser Tyr Gly Gly Leu Ala  
 145 150 155 160

Phe Leu Ser Leu Glu Ala Leu Glu Gly Leu Pro Gly Leu Val Thr Leu  
 165 170 175

Gln Ile Gly Gly Asn Pro Trp Val Cys Gly Cys Thr Met Glu Pro Leu  
 180 185 190

Leu Lys Trp Leu Arg Asn Arg Ile Gln Arg Cys Thr Ala Glu Ser Gly  
 195 200 205

Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg  
 210 215 220

Ala Ala Val Glu Phe Gln Asp Leu Met Gln Leu Gln Asp Leu Asp Leu  
 225 230 235 240

Ser Tyr Glu Asn Leu Ala Phe Leu Lys Leu Lys Ala Leu Ser Ser Val  
 245 250 255

Asn Phe Gly His Arg Gln Ala Val Val Gly Gly Leu Ser Asn Pro Leu  
 260 265 270



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Ser Phe Pro Gly Tyr Leu Thr Leu Pro Gly Phe Cys Val Thr Asp Ser  
 275 280 285

Gln Leu Ala Glu Cys Arg Gly Pro Pro Glu Val Glu Gly Ala Pro Leu  
 290 295 300

Phe Ser Leu Thr Glu Glu Ser Phe Lys Ala Cys His Leu Thr Leu Thr  
 305 310 315 320

Leu Asp Asp Tyr Leu Phe Ile Ala Phe Val Gly Phe Val Val Ser Ile  
 325 330 335

Ala Ser Val Ala Thr Asn Phe Leu Leu Gly Ile Thr Ala Asn Cys Cys  
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His Arg Trp Ser Lys Ala Ser Glu Glu Glu Ile  
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<210> 202  
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<400> 202  
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 1 5 10 15

ttc act gaa tat cct gaa tgg gca ctc cct ctc ttc ctc ttg ttt tta 96  
 Phe Thr Glu Tyr Pro Glu Trp Ala Leu Pro Leu Phe Leu Leu Phe Leu  
 20 25 30

ttt atg tat ctc atc acc gta ttg ggg aac tta gag atg att att ctg 144  
 Phe Met Tyr Leu Ile Thr Val Leu Gly Asn Leu Glu Met Ile Ile Leu  
 35 40 45

atc ctc atg gat cac cag ctc cac gct cca atg tat ttc ctt ctg agt 192  
 Ile Leu Met Asp His Gln Leu His Ala Pro Met Tyr Phe Leu Leu Ser  
 50 55 60

cac ctc gct ttc atg gac gtc tgc tac tca tct atc act gtc ccc cag 240  
 His Leu Ala Phe Met Asp Val Cys Tyr Ser Ser Ile Thr Val Pro Gln  
 65 70 75 80

atg ctg gca gtg ctg ctg gag cat ggg gca gct tta tct tac aca cgc 288  
 Met Leu Ala Val Leu Leu Glu His Gly Ala Ala Leu Ser Tyr Thr Arg  
 85 90 95

tgt gct gct cag ttc ttt ctg ttc acc ttc ttt ggt tcc atc gac tgc 336  
 Cys Ala Ala Gln Phe Phe Leu Phe Thr Phe Phe Gly Ser Ile Asp Cys  
 100 105 110

tac ctc ttg gcc ctc atg gcc tat gac cgc tac ttg gct gtg tgc cag 384  
 Tyr Leu Leu Ala Leu Met Ala Tyr Asp Arg Tyr Leu Ala Val Cys Gln  
 115 120 125

ccc ctg ctt tat gtc acc atc ctg aca cag cag gcc cgc ttg agt ctt 432  
 Pro Leu Leu Tyr Val Thr Ile Leu Thr Gln Gln Ala Arg Leu Ser Leu  
 130 135 140

gtg gct ggg gct tac gtt gct ggt ctc atc agt gcc ttg gtg cgg aca 480  
 Val Ala Gly Ala Tyr Val Ala Gly Leu Ile Ser Ala Leu Val Arg Thr  
 145 150 155 160

gtc tca gcc ttc act ctc tcc ttc tgt gga acc agt gag att gac ttt 528  
 Val Ser Ala Phe Thr Leu Ser Phe Cys Gly Thr Ser Glu Ile Asp Phe  
 165 170 175

att ttc tgt gac ctc cct cct ctg tta aag ttg acc tgt ggg gag agc 576  
 Ile Phe Cys Asp Leu Pro Pro Leu Leu Lys Leu Thr Cys Gly Glu Ser  
 180 185 190

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tac act caa gaa gtg ctg att att atg ttt gcc att ttt gtc atc cct 624  
 Tyr Thr Gln Glu Val Leu Ile Ile Met Phe Ala Ile Phe Val Ile Pro  
 195 200 205  
 gct tcc atg gtg gtg atc ttg gtg tcc tac ctg ttt atc atc gtg gcc 672  
 Ala Ser Met Val Val Ile Leu Val Ser Tyr Leu Phe Ile Ile Val Ala  
 210 215 220  
 atc atg ggg atc cct gct gga agc cag gcc aag acc ttc tcc acc tgc 720  
 Ile Met Gly Ile Pro Ala Gly Ser Gln Ala Lys Thr Phe Ser Thr Cys  
 225 230 235 240  
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 260 265 270  
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 Val Ser Val Leu Tyr Thr Glu Val Ile Pro Met Leu Asn Pro Leu Ile  
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 130 135 140  
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 145 150 155 160

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Val Ser Ala Phe Thr Leu Ser Phe Cys Gly Thr Ser Glu Ile Asp Phe  
165 170 175

Ile Phe Cys Asp Leu Pro Pro Leu Leu Lys Leu Thr Cys Gly Glu Ser  
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Tyr Thr Gln Glu Val Leu Ile Ile Met Phe Ala Ile Phe Val Ile Pro  
195 200 205

Ala Ser Met Val Val Ile Leu Val Ser Tyr Leu Phe Ile Ile Val Ala  
210 215 220

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225 230 235 240

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245 250 255

Met Tyr Leu Arg Gly Asn Ser Asp Gln Ser Ser Glu Lys Asn Arg Val  
260 265 270

Val Ser Val Leu Tyr Thr Glu Val Ile Pro Met Leu Asn Pro Leu Ile  
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cag gtt ggt cca gca ctg gag att ctc ctc tgt gga ctt ttc tct gcc 96  
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Phe Tyr Thr Leu Thr Leu Leu Gly Asn Gly Val Ile Phe Gly Ile Ile  
35 40 45

tgc ctg gac tgt aag ctt cac aca ccc atg tac ttc ttc ctg tca cac 192  
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65 70 75 80

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ata atg cag aca ttc ttg tat ttg gct ttt gct cac gta gag tgt ctg 336  
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100 105 160 200 PCT FINAL.ST25  
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tta cgt tac aat agc ctc atg agc tgg aga gtg tgc act gtc ctg gct 432  
leu arg tyr asn ser leu met ser trp arg val cys thr val leu ala  
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gtg gct tcc tgg gtg ttc agc ttc ctc ctg gct ctg gtc cct tta gtt 480  
val ala ser trp val phe ser phe leu leu ala leu val pro leu val  
145 150 155 160

ctc atc ctg agc ctg ccc ttc tgc ggg cct cat gaa atc aac cac ttc 528  
leu ile leu ser leu pro phe cys gly pro his glu ile asn his phe  
165 170 175

ttc tgt gaa atc ctg tct gtc ctc aag ttg gcc tgt gct gac acc tgg 576  
phe cys glu ile leu ser val leu lys leu ala cys ala asp thr trp  
180 185 190

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pro leu cys leu val leu val ser tyr leu arg ile leu ala ala ile  
210 215 220

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225 230 235 240

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acg tac atg gcc ccc aag tcc cgc cat cct gag gag cag cag aaa gtt 816  
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260 265 270

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tat agc cta agg aat gca gag gtc aag ggc gcc ctg agg agg gca ctg 912  
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Phe Tyr Thr Leu Thr Leu Leu Gly Asn Gly Val Ile Phe Gly Ile Ile  
35 40 45

Cys Leu Asp Cys Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser His  
50 55 60

Leu Ala Ile Val Asp Ile Ser Tyr Ala Ser Asn Tyr Val Pro Lys Met

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16U 200 PCT FINAL.ST25  
 Ile Ser Asn Tyr Pro Gln Trp Arg Asp Thr Phe Phe Thr Leu Val Leu  
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 ata att tac ctc agc aca ttg ttg ggg aat gga ttt atg atc ttt ctt 144  
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 Cys Leu Ala Gln Thr Ser Val Ser Leu Ala Leu Ala Thr Ala Glu Cys  
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&lt;213&gt; Homo sapiens

&lt;400&gt; 219

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Ala Leu Val His Cys Phe Ser Thr His Pro Tyr Leu Ser Tyr Pro Arg  
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Cys Leu Ala Gln Thr Ser Val Ser Leu Ala Leu Ala Thr Ala Glu Cys  
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Ala Cys Glu Ile Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser  
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Ile Arg Ile Arg Ser Leu Gln Gly Arg Leu Lys Ala Phe Thr Thr Cys  
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Gly Ser His Leu Thr Val Val Thr Ile Phe Tyr Gly Ser Ala Ile Ser  
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Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val  
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Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly  
115 120 125  
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145 150 155 160  
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165 170 175  
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180 185 190  
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Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met  
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225 230 235 240  
ttc ctt atc act ggc att gtg cag gtg gcc tgc cag gag tgt cac ctc 768  
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 275 280 285

cag ctc tac cac atg gcc cta gga gtg aag aag gtg ctc acc tca ttc 912  
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 290 295 300

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 305 310 315 320

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Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp  
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Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu  
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Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val  
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 100 105 110

Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly  
 115 120 125

Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro  
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Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val  
 145 150 155 160

Phe His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro  
 165 170 175

Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala  
 180 185 190

Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met  
 195 200 205

16U 200 PCT FINAL.ST25

Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu  
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Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro  
 225 230 235 240

Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu  
 245 250 255

Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser  
 260 265 270

Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu  
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 Ala Ala Glu Ala Ala Gly Ala Pro Asp Arg Val Gly Ser Leu Phe Val  
 35 40 45  
 aaa aaa gtg caa gac gtc cat gct gta gag att agt gcg ttt cga tgt 192  
 Lys Lys Val Gln Asp Val His Ala Val Glu Ile Ser Ala Phe Arg Cys  
 50 55 60  
 gtg ttc caa atg cta gtt gtt atc cct tgc tta ata tac aga aaa act 240  
 Val Phe Gln Met Leu Val Val Ile Pro Cys Leu Ile Tyr Arg Lys Thr  
 65 70 75 80  
 ggg ttt ata ggc cca aaa ggt caa cga att ttc ctc att ctc aga gga 288  
 Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly  
 85 90 95  
 gtc ctt ggt tct acc gcc atg atg ctt ata tac tat gct tac cag aca 336  
 Val Leu Gly Ser Thr Ala Met Met Leu Ile Tyr Tyr Ala Tyr Gln Thr  
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 atg tcc ctc gct gat gcc aca gtt atc acg ttt agc agt cca gtg ttt 384  
 Met Ser Leu Ala Asp Ala Thr Val Ile Thr Phe Ser Ser Pro Val Phe  
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160 200 PCT FINAL.ST25  
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180 185 190

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768  
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245 250 255

816  
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260 265 270

864  
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Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly

85 16U 200 PCT FINAL.ST25  
90 95

Val Leu Gly Ser Thr Ala Met Met Leu Ile Tyr Tyr Ala Tyr Gln Thr  
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Thr Ser Ile Phe Ala Trp Ile Cys Leu Lys Glu Lys Tyr Ser Pro Trp  
130 135 140

Asp Ala Leu Phe Thr Val Phe Thr Ile Thr Gly Val Ile Leu Ile Val  
145 150 155 160

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165 170 175

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Ser Val Ile Ile Leu Ser Val Leu Gly Glu Trp Ser Leu Pro Tyr Cys  
225 230 235 240

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 145 150 155 160

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Cys Gly Phe Cys Val Pro Ile Met Thr Val Met Thr Asp Val Ile Leu  
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Ser Gln Asp Ala Arg Gln Lys Ala Leu Cys Ser Cys Gly Ser His Val  
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Cys Val Ile Leu Ile Phe Tyr Ile Pro Ala Phe Phe Ser Ile Leu Ala  
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His Cys Phe Gly His Asn Val Pro His Thr Phe His Ile Met Phe Ala  
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Asn Leu Tyr Val Ile Ile Pro Pro Ala Leu Asn Ser Ile Val Tyr Arg  
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Gln Phe Leu Ser His Gly Arg Ser Arg Asp His Ala Ile Ala Ala Ile  
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160 200 PCT FINAL.ST25

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atg acc acc aac ttg gat ctg aag gta tcc atg ctc agc ttc atc tca 227  
Met Thr Thr Asn Leu Asp Leu Lys Val Ser Met Leu Ser Phe Ile Ser  
1 5 10 15

gct acc tgc ttg ctc ctc tgc ctc aac ctg ttt gtg gca cag gtt cac 275  
Ala Thr Cys Leu Leu Leu Cys Leu Asn Leu Phe Val Ala Gln Val His  
20 25 30

tgg cat act agg gat gcc atg gag tca gat ctc cta tgg acc tat tat 323  
Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr  
35 40 45

ctt aac tgg tgc agt gac atc ttt tac atg ttt gct ggg atc atc tct 371  
Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser  
50 55 60

ctt ctc aac tac tta act tcc aga tgc cct gcc tgt gat gaa aac gtc 419

16U 200 PCT FINAL.ST25  
 Leu Leu Asn Tyr Leu Thr Ser Arg Ser Pro Ala Cys Asp Glu Asn Val  
 65 70 75 80

act gtg att cca aca gag aga tca agg ctg ggg gtt ggt ccg gtg act 467  
 Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr  
 85 90 95

aca gta tca cct gct aaa gat gaa ggg cca agg tct gag atg gaa tct 515  
 Thr Val Ser Pro Ala Lys Asp Glu Gly Pro Arg Ser Glu Met Glu Ser  
 100 105 110

cta agt gtg aga gag aaa aat tta cca aag tca gga ctg tgg tgg 560  
 Leu Ser Val Arg Glu Lys Asn Leu Pro Lys Ser Gly Leu Trp Trp  
 115 120 125

tgataggaaa acctaactat agcttgcttt aaaagcaggg gagaagctga gttgggaatg 620  
 gtcacataaa ttctgggaaa ctctcctaata atcatgtcca tattacttga ggagacagca 680  
 ttaaagctga tgaatgtct ttgctgtca ttggatccaa aatatatatg atagtcataa 740  
 agtaaataac tcaactaaga aaaacatttc taaaagaaaa caacaatggt tagagtcag 800  
 aatgaaagaa actagtgaag gatgcagtggt gtagaccaga gacctctttg ggtatcaggg 860  
 atctcatgga ccagaatggc ccgtggagaa gaatgttaata tacttctgtt tggaattttc 920  
 ttattatgt gtggctttgg gtatactcag gatggaaagc acttggacaa atactgttga 980  
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<210> 235  
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 <213> Homo sapiens

<400> 235

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Ala Thr Cys Leu Leu Leu Cys Leu Asn Leu Phe Val Ala Gln Val His  
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Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr  
 35 40 45

Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser  
 50 55 60

Leu Leu Asn Tyr Leu Thr Ser Arg Ser Pro Ala Cys Asp Glu Asn Val  
 65 70 75 80

Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr  
 85 90 95

Thr Val Ser Pro Ala Lys Asp Glu Gly Pro Arg Ser Glu Met Glu Ser  
 100 105 110

Leu Ser Val Arg Glu Lys Asn Leu Pro Lys Ser Gly Leu Trp Trp  
 115 120 125

<210> 236  
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16U 200 PCT FINAL.ST25

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&lt;400&gt; 236

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ccaggcactc tagtaggcct ggctaccca gaaacagcag gagagagaag aaacaggcca      120
gctgtgagaa gccaaaggaca ccgagtcagt c atg gca cct aag gcg gca aag      172
                               Met Ala Pro Lys Ala Ala Lys
                               1                               5

ggg gcc aag cca gag cca gca cca gct cca cct cca ccc ggg gcc aaa      220
Gly Ala Lys Pro Glu Pro Ala Pro Ala Pro Pro Pro Pro Gly Ala Lys
                               10                               15                               20

ccc gag gaa gac aag aag gac ggt aag gag cca tct gac aaa cct caa      268
Pro Glu Glu Asp Lys Lys Asp Gly Lys Glu Pro Ser Asp Lys Pro Gln
                               25                               30                               35

aag gcg gtg cag gac cat aag gag cca tct gac aaa cct caa aag gcg      316
Lys Ala Val Gln Asp His Lys Glu Pro Ser Asp Lys Pro Gln Lys Ala
                               40                               45                               50                               55

gtg cag ccc aag cac gaa gtg ggc acg agg agg ggg tgt cgc cgc tac      364
Val Gln Pro Lys His Glu Val Gly Thr Arg Arg Gly Cys Arg Arg Tyr
                               60                               65                               70

cgg tgg gaa tta aaa gac agc aat aaa gag ttc tgg ctc ttg ggg cac      412
Arg Trp Glu Leu Lys Asp Ser Asn Lys Glu Phe Trp Leu Leu Gly His
                               75                               80                               85

gct gag atc aag att cgg agt ttg ggc tgc cta ata gct gca atg ata      460
Ala Glu Ile Lys Ile Arg Ser Leu Gly Cys Leu Ile Ala Ala Met Ile
                               90                               95                               100

ctg ttg tcc tca ctc acc gtg cac ccc atc ttg agg ctt atc atc acc      508
Leu Leu Ser Ser Leu Thr Val His Pro Ile Leu Arg Leu Ile Ile Thr
                               105                               110                               115

atg gag ata tcc ttc ttc agc ttc ttc atc tta ctg tac agc ttt gcc      556
Met Glu Ile Ser Phe Phe Ser Phe Phe Ile Leu Leu Tyr Ser Phe Ala
                               120                               125                               130                               135

att cat aga tac ata ccc ttc atc ctg tgg ccc att tct gac ctc ttc      604
Ile His Arg Tyr Ile Pro Phe Ile Leu Trp Pro Ile Ser Asp Leu Phe
                               140                               145                               150

aac gac ctg att gct tgt gcg ttc ctt gtg gga gcc gtg gtc ttt gct      652
Asn Asp Leu Ile Ala Cys Ala Phe Leu Val Gly Ala Val Val Phe Ala
                               155                               160                               165

gtg aga agt cgg cga tcc atg aat ctc cac tac tta ctt gct gtg atc      700
Val Arg Ser Arg Arg Ser Met Asn Leu His Tyr Leu Leu Ala Val Ile
                               170                               175                               180

ctt att ggt gcg gct gga gtt ttt gct ttt atc gat gtg tgt ctt caa      748
Leu Ile Gly Ala Ala Gly Val Phe Ala Phe Ile Asp Val Cys Leu Gln
                               185                               190                               195

aga aac cac ttc aga ggc aag aag gcc aaa aag cat atg ctg gtt cct      796
-Arg Asn His Phe Arg Gly Lys Lys Ala Lys Lys His Met Leu Val Pro
                               200                               205                               210                               215

cct cca gga aag gaa aaa gga ccc cag cag ggc aag gga cca gaa ccc      844
Pro Pro Gly Lys Glu Lys Gly Pro Gln Gln Gly Lys Gly Pro Glu Pro
                               220                               225                               230

gcc aag cca cca gaa cct ggc aag cca cca ggg cca gca aag gga aag      892
Ala Lys Pro Pro Glu Pro Gly Lys Pro Pro Gly Pro Ala Lys Gly Lys
                               235                               240                               245

aaa tgacttgag gaggtcctg gtgtctgaaa cggcagtgta ttttacagca      945
Lys

atatgtttcc actctcttcc ttgtcttctt tctggaatgg ttttcttttc catttcatt      1005

accacctttg cttggaaaag aatggattaa tggattctaa aagcctaa      1054

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16U 200 PCT FINAL.ST25

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<400> 237

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 35 40 45

Ser Asp Lys Pro Gln Lys Ala Val Gln Pro Lys His Glu Val Gly Thr  
 50 55 60

Arg Arg Gly Cys Arg Arg Tyr Arg Trp Glu Leu Lys Asp Ser Asn Lys  
 65 70 75 80

Glu Phe Trp Leu Leu Gly His Ala Glu Ile Lys Ile Arg Ser Leu Gly  
 85 90 95

Cys Leu Ile Ala Ala Met Ile Leu Leu Ser Ser Leu Thr Val His Pro  
 100 105 110

Ile Leu Arg Leu Ile Ile Thr Met Glu Ile Ser Phe Phe Ser Phe Phe  
 115 120 125

Ile Leu Leu Tyr Ser Phe Ala Ile His Arg Tyr Ile Pro Phe Ile Leu  
 130 135 140

Trp Pro Ile Ser Asp Leu Phe Asn Asp Leu Ile Ala Cys Ala Phe Leu  
 145 150 155 160

Val Gly Ala Val Val Phe Ala Val Arg Ser Arg Arg Ser Met Asn Leu  
 165 170 175

His Tyr Leu Leu Ala Val Ile Leu Ile Gly Ala Ala Gly Val Phe Ala  
 180 185 190

Phe Ile Asp Val Cys Leu Gln Arg Asn His Phe Arg Gly Lys Lys Ala  
 195 200 205

Lys Lys His Met Leu Val Pro Pro Pro Gly Lys Glu Lys Gly Pro Gln  
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Gln Gly Lys Gly Pro Glu Pro Ala Lys Pro Pro Glu Pro Gly Lys Pro  
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Pro Gly Pro Ala Lys Gly Lys Lys  
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<210> 238  
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16U 200 PCT FINAL.ST25

&lt;222&gt; (17) .. (418)

&lt;223&gt;

&lt;400&gt; 238

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ctt ctg ctg ttg ctt agc aac tgg ttg gtc aag tat gaa cac aag ctc 100  
 Leu Leu Leu Leu Ser Asn Trp Leu Val Lys Tyr Glu His Lys Leu  
 15 20 25

acc ctc cca gag ccc cag cag gag gaa gag aaa cca aag act tct gaa 148  
 Thr Leu Pro Glu Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu  
 30 35 40

aac gac tcc aag aac agc aag gcc gtg aac aca aaa gaa gtc aat aga 196  
 Asn Asp Ser Lys Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg  
 45 50 55 60

acg cat gcc tgc ttt gcc ctc cag gac gag atc ctc caa cgg ctg ttg 244  
 Thr His Ala Cys Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu  
 65 70 75

ttc agt gaa atg aag atg aag gtc cta gaa aat cag atg ttc atc ata 292  
 Phe Ser Glu Met Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile  
 80 85 90

tgg aat aaa atg aat cac cac ggg cgg tca agc aga cat cgg aat ttt 340  
 Trp Asn Lys Met Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe  
 95 100 105

ccc atg aaa aaa cac aga atg agg agg cat gag tca att tgc ccc acc 388  
 Pro Met Lys Lys His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr  
 110 115 120

ctg tct gac tgt act tcg agt tcc ccc agc taatgaggcc gaggcgggct 436  
 Leu Ser Asp Cys Thr Ser Ser Pro Ser  
 125 130

ggcctctgcc gatgttacct tttacctcag taaaaccag tcacagcct 487

&lt;210&gt; 239

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 239

Met Ser Tyr Lys Pro Ala Leu Phe Gly Phe Leu Phe Leu Leu Leu Leu  
 1 5 10 15

Leu Ser Asn Trp Leu Val Lys Tyr Glu His Lys Leu Thr Leu Pro Glu  
 20 25 30

Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu Asn Asp Ser Lys  
 35 40 45

Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg Thr His Ala Cys  
 50 55 60

Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu Phe Ser Glu Met  
 65 70 75 80

Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile Trp Asn Lys Met  
 85 90 95

Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe Pro Met Lys Lys  
 100 105 110

His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr Leu Ser Asp Cys

115

120

16U 200 PCT FINAL.ST25  
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                               Met Asp Ser
                               1
caa cag gag gac ctg cgc ttc cct ggg atg tgg gtc tca ttg tac ttt      164
Gln Gln Glu Asp Leu Arg Phe Pro Gly Met Trp Val Ser Leu Tyr Phe
   5                               10                               15
gga atc ctg ggg ctg tgt tct gtg ata act gga ggg tgc att atc ttt      212
Gly Ile Leu Gly Leu Cys Ser Val Ile Thr Gly Gly Cys Ile Ile Phe
  20                               25                               30                               35
ctg cac tgg agg aag aac ttg agg cgg gaa gag cat gcc cag cag tgg      260
Leu His Trp Arg Lys Asn Leu Arg Arg Glu Glu His Ala Gln Gln Trp
                               40                               45                               50
gtg gag gtg atg aga gct gcc aca ttc acc tac agc cca ttg ttg tac      308
Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro Leu Leu Tyr
   55                               60                               65
tgg att aac aag cga cgg cgc tac ggc atg aat gca gcc atc aac acg      356
Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala Ile Asn Thr
   70                               75                               80
ggc cct gcc cct gct gtc acc aag act gag act gag gtc cag aat cca      404
Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val Gln Asn Pro
   85                               90                               95
gat gtt ctg tgg gat ttg gac atc ccc gaa ggc agg agc cat gct gac      452
Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser His Ala Asp
  100                               105                               110                               115
caa gac agc aac ccc aag gcg gaa gcc cct gct ccc ctg caa cct gca      500
Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu Gln Pro Ala
                               120                               125                               130
ctg cag ctg gct cca cag cag ccc cag gcc aga tcc cca ttc cca ctt      548
Leu Gln Leu Ala Pro Gln Gln Pro Gln Ala Arg Ser Pro Phe Pro Leu
  135                               140                               145
-ccc atc ttt cag gag gtg ccc ttt gcc cca ccc ttg tgc aac cta ccc      596
Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys Asn Leu Pro
  150                               155                               160
ccc ctg ctg aac cac tct gtc tcc tat cct ttg gcc acc tgt cct gaa      644
Pro Leu Leu Asn His Ser Val Ser Tyr Pro Leu Ala Thr Cys Pro Glu
  165                               170                               175
agg aat gtt ctc ttc cat tcc ctc ctg aat ctg gcc cag gaa gac cat      692
Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln Glu Asp His
  180                               185                               190                               195
agc ttc aat gcc aag cct ttt cct tca gaa ctg tagcctctc tcaactgaagg      745
Ser Phe Asn Ala Lys Pro Phe Pro Ser Glu Leu
  200                               205
tgggagctgc aggaatcagg tgcagagtag gaaatggaac taacctcagg aaggtggtat      805
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16U 200 PCT FINAL.ST25

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Leu Tyr Phe Gly Ile Leu Gly Leu Cys Ser Val Ile Thr Gly Gly Cys  
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Ile Ile Phe Leu His Trp Arg Lys Asn Leu Arg Arg Glu Glu His Ala  
 35 40 45

Gln Gln Trp Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro  
 50 55 60

Leu Leu Tyr Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala  
 65 70 75 80

Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val  
 85 90 95

Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser  
 100 105 110

His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu  
 115 120 125

Gln Pro Ala Leu Gln Leu Ala Pro Gln Gln Pro Gln Ala Arg Ser Pro  
 130 135 140

Phe Pro Leu Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys  
 145 150 155 160

Asn Leu Pro Pro Leu Leu Asn His Ser Val Ser Tyr Pro Leu Ala Thr  
 165 170 175

Cys Pro Glu Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln  
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Glu Asp His Ser Phe Asn Ala Lys Pro Phe Pro Ser Glu Leu  
 195 200 205

<210> 242  
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 <222> (40)..(585)  
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 1 5

gac aac ctc tta gag tct ctc tct ctc agc aca gta tgg aat tgg ata 102  
 Asp Asn Leu Leu Glu Ser Leu Ser Leu Ser Thr Val Trp Asn Trp Ile  
 10 15 20

## 16U 200 PCT FINAL.ST25

caa gca agt ttt ttg gga gag act agt gca cct cag caa aca agt ttg 150  
 Gln Ala Ser Phe Leu Gly Glu Thr Ser Ala Pro Gln Gln Thr Ser Leu  
 25 30 35

gga cta tta gat aat ctt gct cca gct gtg caa atc atc ttg agg att 198  
 Gly Leu Leu Asp Asn Leu Ala Val Gln Ile Ile Leu Arg Ile  
 40 45 50

tct ttc ttg att tta ttg gga ata gga ata tat gcc tta tgg aaa cga 246  
 Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr Ala Leu Trp Lys Arg  
 55 60 65

agt att cag tca att cag aaa aca ttg ttg ttt gta atc aca ctc tac 294  
 Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe Val Ile Thr Leu Tyr  
 70 75 80 85

aaa ctt tac aag aag ggc tca cat att ttt gag gct ttg cta gcc aac 342  
 Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu Ala Leu Leu Ala Asn  
 90 95 100

cca gaa gga agt ggt ctc cga att caa gac aat aat aat ctt ttc ctg 390  
 Pro Glu Gly Ser Gly Leu Arg Ile Gln Asp Asn Asn Asn Leu Phe Leu  
 105 110 115

tcc ttg ggt ctg caa gag aaa att ttg aaa aaa ctt aag aca gtg gaa 438  
 Ser Leu Gly Leu Gln Glu Lys Ile Leu Lys Lys Leu Lys Thr Val Glu  
 120 125 130

aac aaa atg aag aac cta gaa ggg ata atc gtt gct caa aaa cct gcc 486  
 Asn Lys Met Lys Asn Leu Glu Gly Ile Ile Val Ala Gln Lys Pro Ala  
 135 140 145

acg aag agg gat tgc tcc tct gag ccc tac tgc agc tgc tct gac tgc 534  
 Thr Lys Arg Asp Cys Ser Ser Glu Pro Tyr Cys Ser Cys Ser Asp Cys  
 150 155 160 165

cag agt ccc ttg tcc aca tca ggg ttt act tcc ccc att tga aat gtg 582  
 Gln Ser Pro Leu Ser Thr Ser Gly Phe Thr Ser Pro Ile Asn Val  
 170 175 180

atg gactccaatc ttttccagga aagcactggt tccctcatgt gtgcagtggg 635  
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gtatcaataa agatagagaa cgctattg 663

<210> 243  
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 <212> PRT  
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<400> 243

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Gln Gln Thr Ser Leu Gly Leu Leu Asp Asn Leu Ala Pro Ala Val Gln  
 35 40 45

Ile Ile Leu Arg Ile Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr  
 50 55 60

Ala Leu Trp Lys Arg Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe  
 65 70 75 80

Val Ile Thr Leu Tyr Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu  
 85 90 95

16U 200 PCT FINAL.ST25  
 Ala Leu Leu Ala Asn Pro Glu Gly Ser Gly Leu Arg Ile Gln Asp Asn  
 100 105 110

Asn Asn Leu Phe Leu Ser Leu Gly Leu Gln Glu Lys Ile Leu Lys Lys  
 115 120 125

Leu Lys Thr Val Glu Asn Lys Met Lys Asn Leu Glu Gly Ile Ile Val  
 130 135 140

Ala Gln Lys Pro Ala Thr Lys Arg Asp Cys Ser Ser Glu Pro Tyr Cys  
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Pro Ile

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 Met Cys Phe Ala Gly Phe Ser Phe Lys Glu Lys Ile Phe Ile Ala Leu  
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 gca tgg atg ccc aaa gct aca gta cag gct gtg tta ggt cct ctg gct 157  
 Ala Trp Met Pro Lys Ala Thr Val Gln Ala Val Leu Gly Pro Leu Ala  
 20 25 30  
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 Leu Glu Thr Ala Arg Val Ser Ala Pro His Leu Glu Pro Tyr Ala Lys  
 35 40 45  
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 Asp Val Met Ser Val Ala Phe Leu Ala Ile Ser Ile Thr Ala Pro Asn  
 50 55 60  
 gga gct cta ctt atg ggc att ctg ggg cct aaa atg ctt aca cgc cat 301  
 Gly Ala Leu Leu Met Gly Ile Leu Gly Pro Lys Met Leu Thr Arg His  
 65 70 75 80  
 tat gat cca agc aaa ata aaa ctg caa ttg tca aca tta gaa cat cat 349  
 Tyr Asp Pro Ser Lys Ile Lys Leu Gln Leu Ser Thr Leu Glu His His  
 85 90 95  
 taaaaagttt acctgtcatc atctgcctgc ttcttttaat gaattatttc acatgacaga 409  
 agaatttttaa agtagaata tgtagggact gtacagaaaa tccaggattt agtaaacatg 469  
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<210> 245  
 <211> 96  
 <212> PRT  
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## 16U 200 PCT FINAL.ST25

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Leu Glu Thr Ala Arg Val Ser Ala Pro His Leu Glu Pro Tyr Ala Lys  
35 40 45

Asp Val Met Ser Val Ala Phe Leu Ala Ile Ser Ile Thr Ala Pro Asn  
50 55 60

Gly Ala Leu Leu Met Gly Ile Leu Gly Pro Lys Met Leu Thr Arg His  
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Tyr Asp Pro Ser Lys Ile Lys Leu Gln Leu Ser Thr Leu Glu His His  
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<210> 246

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<212> DNA

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<222> (128)..(2284)

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gtgagcc atg ttc gta ggc gtc gcc cgg cac tct ggg agc cag gat gaa 169  
Met Phe Val Gly Val Ala Arg His Ser Gly Ser Gln Asp Glu  
1 5 10

gtc tca agg gga gta gag ccg ctg gag gcc gcg cgg gcc cag cct gct 217  
Val Ser Arg Gly Val Glu Pro Leu Glu Ala Ala Arg Ala Gln Pro Ala  
15 20 25 30

aag gac agg agg gcc aag gga acc ccg aag tcc tcg aag ccc ggg aaa 265  
Lys Asp Arg Arg Ala Lys Gly Thr Pro Lys Ser Ser Lys Pro Gly Lys  
35 40 45

aaa cac cgg tat ctg aga cta ctt cca gag gcc ttg ata agg ttc ggc 313  
Lys His Arg Tyr Leu Arg Leu Leu Pro Glu Ala Leu Ile Arg Phe Gly  
50 55 60

ggt ttc cga aaa agg aaa aaa gcc aag tcc tca gtt tcc aag aag ccg 361  
Gly Phe Arg Lys Arg Lys Lys Ala Lys Ser Ser Val Ser Lys Lys Pro  
65 70 75

gga gaa gtg gat gac agt ttg gag cag ccc tgt ggt ttg ggc tgc tta 409  
Gly Glu Val Asp Asp Ser Leu Glu Gln Pro Cys Gly Leu Gly Cys Leu  
80 85 90

gtc agc acc tgc tgt gag tgt tgc aat aac att cgc tgc ttc atg att 457  
Val Ser Thr Cys Cys Glu Cys Cys Asn Asn Ile Arg Cys Phe Met Ile  
95 100 105 110

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225 230 235

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240 245 250

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320 325 330

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370 375 380

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Phe Ile Ala Phe Tyr Gly Asp Arg Lys Lys Val Ile Trp Phe Val Ala  
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Ser Ser Phe Leu Ile Gly Leu Gly Ser Leu Leu Cys Ala Phe Pro Ser  
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Glu Glu Ile Lys Val Val Ser Gly Cys Gln Ser Ser Gly Ile Ser Phe  
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325 16U 200 PCT FINAL.ST25  
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595 600 605

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160 200 PCT FINAL.ST25

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 675 680 685

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ccc gta tgg ctg gtg cta cag gga ccc agg ctg atg tgg gct ggc atg 342  
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16U 200 PCT FINAL.ST25

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Asp Leu Phe Leu Ser Cys Leu His Gly Leu Met Leu Val Ala Leu Leu  
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Leu Val Val Val Thr Trp Arg Val Cys Gln Lys Ser His Cys Phe Arg  
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16U 200 PCT FINAL.ST25

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 55 60 65 70

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160 200 PCT FINAL.ST25

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Gln Tyr Trp Lys Glu Glu Val His Ile Gln Asp Val Gly Gly Leu Ile  
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Cys Arg Ala Cys Asn Leu Ser Leu Pro Phe His Gly Cys Leu Leu Asp  
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Asn Thr Ser Glu Cys Phe Lys Ser Thr Leu Val Lys Arg Ile Leu Gln  
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Cys Ile Leu Thr Phe Gly Met Val Asn Pro His Met Tyr Tyr Leu Asn	
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Lys Val Met Ser Ser Leu Phe Leu Asp Thr Ser Val Pro Gly Glu Glu	
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Arg Thr Asn Phe Lys Ser Ile Arg Ser Ile Thr Asp Phe Trp Lys Phe	
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Asn Thr Cys Lys Val Tyr Ser Ser Phe Gln Ser Leu Met Ser Glu Cys	
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Tyr Gly Lys Tyr Thr Ser Ala Asn Glu Asp Leu Ser Asn Phe Gly Leu	
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Trp His Trp Gly Phe Leu Gly Val Tyr Arg Asn Gly Gly Tyr Ile Phe	
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Thr Leu Ser Lys Ser Lys Ser Glu Thr Lys Asn Lys Phe Ile Asp Leu	
205 210 215	
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Arg Leu Asn Ser Trp Ile Thr Arg Gly Thr Arg Val Ile Phe Ile Asp	
220 225 230	
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